Changing strategies in diverticulitis

Caroline Suzanne Andeweg

Changing strategies in diverticulitis

Caroline Suzanne Andeweg

Colofon

The research presented in this thesis was performed at the Department of Gastrointestinal Surgery, Radboud University Nijmegen Medical Centre, the Netherlands.

Sponsoring of this thesis was kindly provided by:
Afdeling Heelkunde UMCN – Stichting Surgical Education Harderwijk – Duomed – Gore – Coloplast – KCI-medical – Maatschap chirurgen Noord-West Veluwe

Cover design: Caroline Andeweg
Photo provided by: Johannes Klapwijk
Lay out: Karin Berkhout
Printed by: Gildeprint

ISBN/EAN 9789461089540

Changing strategies in diverticulitis

een wetenschappelijke proeve

op het gebied van de Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de Rector Magnificus,
professor dr. Th.L.M. Engelen,
volgens besluit van het College van Decanen
in het openbaar te verdedigen op 30 april
des namiddags om 14:30 uur precies

door

Caroline Suzanne Andeweg
geboren op 21-08-1975
te Ermelo

Promotor
Prof. dr. H. van Goor

Tweede promotor
Prof. dr. R.P. Bleichrodt

Manuscriptcommissie
Prof. dr. H.G. Gooszen
Prof. dr. W.M. Prokop
Prof. dr. C.J.J. Mulder

Tis a lesson you should heed:

Try, try, try again.

If at first you don't succeed,

Try, try, try again

(Thomas H. Palmer)

Table of contents

PART III

Chapter 1

Introduction and outline of the thesis

Introduction

Patients with acute abdominal pain due to acute colonic diverticulitis (ACD) impose an impressive burden to healthcare.[1] In the Netherlands, patients with ACD account for over 18,000 admissions and expenditures exceed 80 million euro per year. In the past years, a rise in the number of hospitalizations for ACD has been noted in the Netherlands. In 2009, 18,355 patients were hospitalized with ACD as compared to 13,655 patients in 2006.[2, 3] This significant rise in hospital admissions is also notable in other countries. A recent study from the United States showed an increase in hospital admissions during the period 1998-2005 of 26%, with the largest increase in the age between 18 and 44 years.[1] In the Netherlands, 60% of patients admitted to the hospital for ACD are women.[2] This overall difference in incidence of ACD between men and women has also been reported in other countries.[4] Patients younger than 50 years of age with ACD are predominantly men, whereas in the age group of 50-70 years there is a preference for women.[4-8] Patients with mild (recurrent) diverticulitis are usually treated by the general practitioner or on an outpatient basis, which makes it difficult to accurately determine the true incidence and recurrence rates of diverticulitis. It is estimated that approximately 20 to 25% of patients with diverticulosis coli develop ACD.[9]

Pathogenesis of diverticulosis

Diverticula are sac-like outpouchings of the colonic wall. Diverticula arise where the vasa recta penetrate the colonic wall to supply blood to the mucosa of the colon. This is a weak spot and prone for protrusion of the mucosa and submucosa through the muscle layer of the colonic wall. Because colonic diverticula exist of mucosa, and submucosa, which is covered by serosa, they are referred to as false diverticula. This is in contrast to true diverticula, which are diverticula that encompass the complete bowel wall, e.g., a Meckel's diverticulum. Diverticula generally occur in parallel rows along the mesenteric side of the antimesenteric taeniae. With progression, an additional row of diverticula may be found between the antimesenteric taeniae.[10] The common theory, with respect to the development of diverticulosis, focuses on three aspects: structural abnormalities of the colonic wall, motility disorders of the colon, and the role of dietary fiber.[11] In pathological examination of colon specimen, changes in collagen structure, increased deposition of elastin and thickening of the colonic wall were found in patients with diverticulosis coli.[12, 13] Wess et al.[12] analyzed colonic collagen content in an attempt to determine if a lack of collagen is responsible for this apparent weakness of the muscular wall. As the collagen content does not change with age or the presence of diverticula, the changes are more likely to be qualitative than quantitative. Collagen fibrils demonstrate increased cross-linking with increased age; this process seems to increase most dramatically after 40 years of age, the age at which the incidence of diverticulosis also appears to increase. This same study demonstrated that patients with diverticulosis have an abnormally high

amount of collagen cross-linkage in the colon wall. This increased cross-linkage likely causes the tissues to become stiffer, less resistant to stretching and results in wall thickening. Wall thickening leads to reduction of the intraluminal volume and increase in intraluminal pressure, which probably is the key factor in the development of diverticula.[14, 15]

It has also been suggested that the colon in patients with diverticulosis functions not as a tube, but as individual compartments generating high pressures, a process called segmentation. The high pressures resulting from segmentation may lead to the focal muscular atrophy and subsequent mucosal herniation.[16] Diverticula occur most frequently in the sigmoid colon because the lumen of the colon is the narrowest resulting in the generation of the highest pressures.

Diverticulosis coli is often called a disease of Western civilization because of the relation between lack of fiber in the diet and the pathogenesis of the disease. Dietary fibers are not digested and stimulate and activate the peristalsis of the colon to create voluminous stool. Subsequently the colon has to deal with larger amounts of stool and dilates leading to less segmentation, with a decrease of the intracolonic pressure as a result. A large population based study supports the positive effect of the use of dietary fiber to prevent the development of diverticulosis coli. The risk of the development of diverticulosis coli was inversely associated with insoluble dietary fiber intake.[17]

Definitions

The term ‘diverticular disease’ used in Anglo Saxon literature comprises a spectrum of conditions that are all related to diverticulosis of the colon. Some use the term diverticular disease for patients having symptoms associated with diverticulosis and distinguish diverticulitis as a different entity, whereas others include diverticulitis and diverticular bleeding in the term ‘diverticular disease’. The lack of uniformity in terminology results in difficulties interpreting and comparing findings between studies. It seems best to use the term ‘diverticulosis coli’ and to distinguish between uncomplicated and complicated diverticulosis.

Uncomplicated diverticulosis

Patients with uncomplicated diverticulosis coli have no symptoms, which makes it difficult to determine the true prevalence. Based on autopsy reports from the 60s diverticulosis is present in about 50% of patients older than 80 years.[15, 18] The prevalence of diverticulosis coli depends on age and increases from about 5% around the age of forty to 30% around sixty and 65% around eighty-five years without gender differences.

Complicated diverticulosis coli
Complicated diverticulosis coli encompasses the complete spectrum of symptoms that can arise in patients with diverticulosis coli. This includes patients with (chronic) persistent abdominal pain, acute colonic diverticulitis and diverticular bleeding.

Acute colonic diverticulitis (ACD)
Acute colonic diverticulitis refers to inflammation of diverticula and has a wide variety of clinical presentations varying from mild to severe complicated disease. Uncomplicated diverticulitis is referred to when the inflammation of one or more diverticula leads to an inflammatory process without perforation or abscess formation. Complicated diverticulitis is associated with abscess formation, perforation or fistula formation. Recurrent episodes of diverticulitis can result in stenosis and obstruction or fistula to nearby organs (mostly bladder) or the skin.

Pathogenesis of acute colonic diverticulitis

There are several theories about the pathogenesis of ACD of which no one has been evidently confirmed. It was believed that obstructive fecal matter in the diverticulum leads to an increased pressure of the diverticular sac, resulting in vascular compromise with necrosis and micro or macro perforation of the diverticulum. Due to the localization of the diverticula on the mesenteric side of the bowel, this gives rise to the inflammation of the pericolonic mesenteric fat. Why some patients with diverticulosis will remain asymptomatic, while others develop diverticulitis is unknown. More recent studies suggest changes in colonic flora and the existence of a local low-grade mucosal infection in patients with diverticulitis.[21] This low-grade infection is an explanation for the histological findings of chronic inflammation in patients operated for recurrent episodes of diverticulitis. Additionally, low grade infection may be an explanation for patients who experience persistent abdominal pain after an episode of diverticulitis, comparable with periods of exacerbation and remission in patients with inflammatory bowel disease.

Classification of acute colonic diverticulitis

Hinchey proposed a clinical scoring system in 1978 to classify acute colonic diverticulitis and a modified version is still used in clinical practice.[22, 23] (*Table 1*)

Table 1: Modified Hinchey classification and accompanying CT findings according to Kaiser

Modified Hinchey classification		Accompanying CT findings
Stage 0	Clinically mild diverticulitis	Diverticuli with or without colonic wall thickening
Stage Ia	Confined pericolic inflammation or phlegmon	Colonic wall thickening with inflammatory reaction in pericolic fatty tissue
Stage Ib	Abscess formation (<5cm) in the proximity of the primary inflammatory process	Alterations as stage Ia + pericolic or mesocolic abscess
Stage II	Intra-abdominal abscess, pelvic or retroperitoneal abscess, abscess distant from the primary inflammatory process	Alteration as stage Ia + distant abscess formation (mostly pelvic or interloop abscesses)
Stage III	Generalized purulent peritonitis	Free gas with localized or generalized free fluid and possible thickening of the peritoneum
Stage IV	Generalized faecal peritonitis	Similar findings to stage III

Clinical diagnosis and imaging

Patients with acute abdominal pain in the lower left abdomen, fever and an elevated white blood cell count are suspected of having ACD. Clinical evaluation alone seems inadequate to make the diagnosis; several studies show that the clinical diagnosis of ACD is wrong in 34% to 68% of suspected cases.[24-26] The lack of specific signs and symptoms for accurately establishing the clinical diagnosis of patients with ACD and the discrepancy between the clinical and perioperative findings in patients with the presumptive diagnosis ACD, demanded for good imaging modalities to diagnose ACD. The radiological investigations that have been used for the diagnosis of acute diverticulitis are plain water-soluble contrast enema, ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI). Colonoscopy is rarely used for diagnostic purposes in the acute setting.

The use of water-soluble contrast enema is considered an obsolete imaging technique of depicting ACD. Although proven a safe and feasible technique in the past, water-soluble enema only depicts intraluminal details, whereas ACD is mainly characterized by extramural inflammation.

The most common US technique used to examine patients with suspected ACD is the graded compression technique. With this technique interposing fat and bowel can be displaced or compressed to show underlying structures. If the bowel cannot be compressed, the non-compressibility itself is a sign of inflammation.[27] US is a real-time dynamic examination with wide availability and easy accessibility. Graded-compression

ultrasound has been widely used to diagnose ACD. Potential drawback is the inter-operator variability.[28, 29]

The use of CT in the evaluation of patients suspected of ACD has increased to a large extent. Modern CT imaging techniques allow us to visualize high-resolution images with a mean scanning time of less than 15 minutes. Exposure to radiation is a well-known disadvantage of CT. One out of 4 patients with diverticulitis will suffer from recurrent episodes of ACD and risk multiple CT scans over time. With the increasing use of CT in patients with diverticulitis the risk of radiation exposure and radiation induced malignancies may be a real concern.[27] With the introduction of CT, radiological classifications for ACD were introduced. Kaiser et al. correlated findings on CT to the modified Hinchey scores, to standardize the reporting of CT imaging in patients with acute colonic diverticulitis.[30] (*Table 1*)

MRI is not widely used in the diagnostic work-up of patients suspected of ACD. Although MRI has demonstrated promising results in terms of sensitivity and specificity in diagnosing ACD, availability and expertise with this examination around the clock are more limited than US and CT.[31]

Whether or not the process of diagnostic decision-making and the role of additional imaging in patients suspected of having ACD can be improved is topic of this thesis and addressed at the end of this chapter.

Treatment

Treatment of ACD depends on the severity of the disease. The majority of patients have uncomplicated ACD and can be treated conservatively. The conservative treatment of uncomplicated diverticulitis is successful in more than 90% of patients with Hinchey 0 and Ia stage of diverticulitis.[30, 32-34] Usually a diet high in fibers, laxatives and bed rest are advised, but none of these treatments is evidence based. Almost all studies in which conservative treatment of patients with Hinchey 0 or Ia diverticulitis is investigated report the use of antibiotics, again without any supporting evidence of clinical effect. Dutch patients with uncomplicated ACD are not routinely treated with antibiotics. The use of antibiotic treatment is reserved for patients with a body temperature >38.5 degrees Celsius, with a clinical deterioration or with signs of bacteremia or sepsis.[35, 36] In about 15%-20% of patients with ACD, complications such as an abscess (Hinchey Ib or II), fistula formation and perforation occurs.[37, 38] Antibiotic treatment of abscesses up to 4-5cm is successful in 73% of the patients.[30, 39-43] If the abscess is larger or antibiotic treatment fails, there is an indication for percutaneous drainage. Antibiotic treatment with percutaneous treatment is successful in 81% of the patients with complicated ACD. Surgical drainage is only indicated when this strategy fails. Perforation of a diverticulum or abscess into the

free abdominal cavity leads to peritonitis with an overall mortality of 14% (Hinchey III or IV). It is a relatively rare complication with a prevalence of approximately 3,5 per 100,000 per year.[37, 38] Peritonitis is a medical emergency and needs urgent treatment. Prevention of sepsis and multiple organ failure by means of rapid resuscitation, the immediate administration of intravenous antibiotics and eliminating the disease process are measures that should be immediately taken.[44] Several studies have shown that resection of the affected portion of the colon has better results than a diverting ileostomy or colostomy alone.[45] In patients who are not seriously ill, are not haemodynamically unstable, and have no serious comorbidity a primary anastomosis after resection is usually safe.[46-48] In other cases a Hartmann's procedure, in which the affected colonic segment is resected with closure of the rectal stump and formation of an end colostomy is performed. Recently, good results of laparoscopic lavage and drainage of the abdominal cavity in patients with a purulent peritonitis (Hinchey III) without resection of the bowel and without applying a diverting ileo- or colostomy have been described. This operative strategy combined with the use of intravenous antibiotics, seems a promising alternative in patients with Hinchey III diverticulitis, although this technique should be evaluated in a randomized trial.[49, 50] Stenosis and fistula formation are late complications of diverticulitis and are an indication for surgery.

The American Society of Colon and Rectal Surgeons (ASCRS) state in their most recent guideline that elective sigmoid resection after recovery from acute diverticulitis should be made on a case-by-case basis.[51] This advice differed significantly from the advice given six years earlier, in which a plea for elective surgery after two episodes of diverticulitis was proposed.[52] Recent data on the natural history of diverticulitis has shown that recurrent episodes of diverticulitis mostly run a benign course and only 5.5% of the patients with recurrent hospitalizations for diverticulitis end up with emergency surgery.[38] Moreover, most patients who present with complicated diverticulitis do so at the time of their first attack.[37, 53-55] Therefore, a policy of elective sigmoid resection after recovery from uncomplicated ACD might not decrease the likelihood of later emergency surgery and the number of previous episodes itself seems no longer an indication for elective sigmoid resection.[56] Persistent colonic symptoms, particularly abdominal pain, have been reported in patients after episodes of diverticulitis. It has been suggested that this pain represents increased visceral sensitivity.[57] These patients might benefit from early colonic resection.

Elective sigmoid resection for complicated diverticulosis can be performed either with an open or laparoscopic approach. Two randomized trials favor laparoscopic surgery over open surgery. In the 'Sigma trial' significantly more complications, higher pain scores and longer hospital stay were found among patients with open surgery. Operating time was significantly longer in the laparoscopic group, with a conversion rate of 19%. Quality of life was significantly better after six weeks, but did not differ after 6 months.[58] The Gervaz study also had equal long-term results, except the cosmetic outcome, which was better in the laparoscopic group. No difference was found considering ventral hernia, patient

satisfaction, quality of life or total costs.[59] Laparoscopic surgery provides a faster functional recovery than an open sigmoid resection and a possibly less risk of complications, but the long-term advantages of laparoscopic sigmoid resection are not evident.

Recently, new theories about similarities between diverticulitis and inflammatory bowel disease have been proposed and good results with medical therapy are being reported. The use of 5-aminosalicylic acid in combination with a non-absorbable antibiotic and the use of probiotics have been described in the reduction of persistent abdominal complaints. Medical treatment has not been proven to reduce recurrent diverticulitis.[60-62]

The role and timing of elective surgery in patients with recurrent ACD is still evolving and remains subject of debate. Whether or not patients with recurrent episodes of diverticulitis or persistent abdominal pain benefit from early surgery or benefit from new medical treatment protocols is addressed in this thesis.

Outline of the thesis

This thesis is divided into three parts. The first part of this thesis (Chapter 2, 3, 4 and 5) addresses clinical decision making in patients with suspected ACD. Chapter 2, 3 and 4 discuss the clinical decision-making in patients with left-sided diverticulitis, while Chapter 5 discusses the potential pitfalls in diagnosing right-sided diverticulitis. The second part of the thesis (Chapter 6, 7 and 8) describes different treatment strategies in patients with recurrent episodes of ACD. The incidence and risk factors of recurrence after surgical treated ACD are discussed separately in chapter 8. In the third part of the thesis, the Dutch National guidelines for diagnosis and treatment of acute colonic diverticulitis are summarized (Chapter 9), and future perspectives are described (Chapter 10).

Part one

Clinical evaluation in patients with ACD seems to be wrong in almost two third of the patients suspected of ACD.[24-26] This led to the idea that the diagnostic process in diverticulitis might be improved by a clinical scoring system, similar to scoring systems that have been proposed for example for patients with acute appendicitis[63] Such a scoring system may ultimately lead to the reduction of additional imaging, especially reducing the number of CT scans. Approximately 25% of the patients with ACD, risk multiple episodes of ACD, and therefore multiple CT scans with an increased risk of radiation-induced malignancies. This widespread use of imaging can probably be reduced to some extent, since approximately 90% of patients with ACD can be managed conservatively.[30] Additional imaging in patients with uncomplicated diverticulitis rarely leads to alterations in management.[50] A scoring system based on clinical symptoms and signs, and basic laboratory parameters, might also reduce costs associated with imaging. In **Chapter 2**, the development of such a scoring system for diverticulitis is described. The diagnostic value

of elements of disease history, physical examination, and routine laboratory tests in patients suspected of ACD were assessed and compared and based on these findings a clinical scoring system, that could predict ACD in clinical practice, was constructed. A letter to the editor with valuable comments and our response are added to this manuscript.

Before any scoring system can be propagated for widespread use it should be tested in other data than in those it was developed (external validation).[64, 65] External validation enhances the general applicability and takes into account historical, geographic and methodological differences.[66] In **Chapter 3** an external validation of the model is done with a comparative Dutch cohort of patients suspected of ACD and with a third independent dataset with patients with acute abdominal pain from a large Swedish database.[67]

The added value of imaging after clinical evaluation, particularly its effect on diagnostic accuracy and certainty and patient treatment, is important and needs to be well defined in the diagnostic work-up of patients suspected of ACD. Additional imaging improves decision making, but there is no consensus on which radiological procedure is preferable. **Chapter 4** describes the complete diagnostic process of patients suspected of ACD at an emergency department or during hospitalization. We systematically reviewed the published literature on clinical decision-making and imaging techniques in patients suspected of ACD and provide an evidence-based step up approach to diagnose diverticulitis.

Right-sided colonic diverticulitis (RCD) is rare in Western patients and is considered a more aggressive disease than left-sided diverticulitis, probably based on a different etiology. RCD most often proved to be an unexpected finding during intended appendectomy in the era before the widespread use of imaging, since the clinical picture of RCD resembles that of acute appendicitis. A colonic resection is normally performed to treat the inflamed colon or exclude a carcinoma. In the last two decades, radiological imaging is standardized in the diagnostic work-up of patients with acute abdominal pain. This resulted in a pivotal shift for left-sided diverticulitis from a clinical to a radiological diagnosis, and for RCD from a surgical to a radiological diagnosis. There are no clinical guidelines for the diagnosis and treatment of Western patients with RCD, but we hypothesized that the natural course of patients with RCD would be similar to patients with acute left-sided diverticulitis. **Chapter 5** describes the clinical course and potential differences in a retrospective cohort of patients with RCD and left-sided diverticulitis.

Part two

Morbidity and mortality rates of operative treatment of diverticulitis and a better understanding of complicated diverticulitis caused a shift towards a more conservative approach in patients with recurrent diverticulitis. However, the optimal treatment strategy for patients with recurrent episodes of diverticulitis remains unclear. The results

of new treatment options in patients with recurrent episodes of diverticulitis might play a more prominent role in the decision whether or not to operate. In **Chapter 6**, a Markov model was designed in which different (surgical and non-surgical) treatment strategies in patients with recurrent episodes of ACD were compared. In the Markov model we aim to determine whether patients would benefit from colonic resection after two or three episodes of diverticulitis, or that conservative or medical treatment after the third episode would be preferable in terms of Quality Adjusted Life Years (QALYs).

Assessment of early morbidity and mortality is not sufficient to establish the optimal treatment strategy in patients with recurrent episodes of ACD. Quality of life (QoL) and other patient reported outcomes (PROs) are increasingly recognized as crucial when determining clinical outcome after medical interventions. Nowadays, PROs should be included in the choice of treatment modality.[68] In **Chapter 7**, the impact of conservative versus operative treatment on QoL and other PROs in patients with recurrent episodes of ACD has been reviewed. In **Chapter 8**, the incidence and risk factors associated with recurrent ACD is addressed in patients who underwent surgery for uncomplicated or complicated diverticulitis. Identifying patients at risk for failure of resectional therapy would help to better select patients for elective surgery.

Part three

A multidisciplinary working group initiated by the Dutch Society of Surgery developed national guidelines concerning the epidemiology, classification, diagnosis and treatment of ACD in all its aspects. This work was inspired by the fact that there is a lot of inconsistent evidence and publications concerning ACD, a disease with a high incidence, but wherein the treatment is merely based on the doctor's personal preference. The guidelines are based on an evidence-based review of the literature and recommendations are based on current scientific evidence. **Chapter 9** summarizes the Dutch National Guidelines for diagnosis and treatment of acute colonic diverticulitis, which can be generalized to all Western countries because the guidelines are based upon international medical literature. In **Chapter 10**, the results and conclusions are summarized in the English and Dutch language, respectively, and future perspectives are described.

Reference list

1 Etzioni DA, Mack TM, Beart RW, and Kaiser AM. Diverticulitis in the United States: 1998-2005: changing patterns of disease and treatment. Ann Surg. 2009, Feb;249(2):210-7.

2 KiwaPrismant. KiwaPrismant. http://www.kiwaprismant.nl

3 Draaisma WA, van de Wall BJ, Vermeulen J, Unlu C, de Korte N, and Swank HA. [Treatment for diverticulitis not thoroughly researched]. Ned Tijdschr Geneeskd. 2009;153A648.

4 Rodkey GV, and Welch CE. Changing patterns in the surgical treatment of diverticular disease. Ann Surg. 1984, Oct;200(4):466-78.

5 Ambrosetti P, Robert JH, Witzig JA, Mirescu D, Mathey P, Borst F, and Rohner A. Acute left colonic diverticulitis in young patients. J Am Coll Surg. 1994, Aug;179(2):156-60.

6 Schauer PR, Ramos R, Ghiatas AA, and Sirinek KR. Virulent diverticular disease in young obese men. Am J Surg. 1992, Nov;164(5):443-6; discussion 446-8.

7 Lahat A, Menachem Y, Avidan B, Yanai H, Sakhnini E, Bardan E, and Bar-Meir S. Diverticulitis in the young patient--is it different ? World J Gastroenterol. 2006, May 14;12(18):2932-5.

8 Acosta JA, Grebenc ML, Doberneck RC, McCarthy JD, and Fry DE. Colonic diverticular disease in patients 40 years old or younger. Am Surg. 1992, Oct;58(10):605-7.

9 Schoetz DJ. Diverticular disease of the colon: a century-old problem. Dis Colon Rectum. 1999, Jun;42(6):703-9.

10 Slack WW. The anatomy, pathology, and some clinical features of divericulitis of the colon. Br J Surg. 1962, Sep;50185-90.

11 Hobson KG, and Roberts PL. Etiology and pathophysiology of diverticular disease. Clin Colon Rectal Surg. 2004, Aug;17(3):147-53.

12 Wess L, Eastwood MA, Wess TJ, Busuttil A, and Miller A. Cross linking of collagen is increased in colonic diverticulosis. Gut. 1995, Jul;37(1):91-4.

13 Whiteway J, and Morson BC. Elastosis in diverticular disease of the sigmoid colon. Gut. 1985, Mar;26(3):258-66.

14 Morson BC. The muscle abnormality in diverticular disease of the colon. Proc R Soc Med. 1963, Sep;56798-800.

15 Hughes LE. Postmortem survey of diverticular disease of the colon. I. Diverticulosis and diverticulitis. Gut. 1969, May;10(5):336-44.

16 Chia JG, Wilde CC, Ngoi SS, Goh PM, and Ong CL. Trends of diverticular disease of the large bowel in a newly developed country. Dis Colon Rectum. 1991, Jun;34(6):498-501.

17 Aldoori WH, Giovannucci EL, Rimm EB, Wing AL, Trichopoulos DV, and Willett WC. A prospective study of diet and the risk of symptomatic diverticular disease in men. Am J Clin Nutr. 1994, Nov;60(5):757-64.

18 Parks TG. Natural history of diverticular disease of the colon. A review of 521 cases. Br Med J. 1969, Dec 13;4(5684):639-42.

19 Painter NS, and Burkitt DP. Diverticular disease of the colon, a 20th century problem. Clin Gastroenterol. 1975, Jan;4(1):3-21.

20 Parks TG. Natural history of diverticular disease of the colon. Clin Gastroenterol. 1975, Jan;4(1):53-69.

21 Floch CL. Diagnosis and management of acute diverticulitis. J Clin Gastroenterol. 2006, Aug;40 Suppl 3S136-44.

22 Hinchey EJ, Schaal PG, and Richards GK. Treatment of perforated diverticular disease of the colon. Adv Surg. 1978;1285-109.
23 Wasvary H, Turfah F, Kadro O, and Beauregard W. Same hospitalization resection for acute diverticulitis. Am Surg. 1999, Jul;65(7):632-5; discussion 636.
24 Wexner SD, and Dailey TH. The initial management of left lower quadrant peritonitis. Dis Colon Rectum. 1986, Oct;29(10):635-8.
25 Cho KC, Morehouse HT, Alterman DD, and Thornhill BA. Sigmoid diverticulitis: diagnostic role of CT--comparison with barium enema studies. Radiology. 1990, Jul;176(1):111-5.
26 Farag Soliman M, Wüstner M, Sturm J, Werner A, Diehl SJ, Düber C, and Post S. [Primary diagnostics of acute diverticulitis of the sigmoid]. Ultraschall Med. 2004, Sep;25(5):342-7.
27 Stoker J, van Randen A, Laméris W, and Boermeester MA. Imaging patients with acute abdominal pain. Radiology. 2009, Oct;253(1):31-46.
28 Zielke A, Hasse C, Nies C, Kisker O, Voss M, Sitter H, and Rothmund M. Prospective evaluation of ultrasonography in acute colonic diverticulitis. Br J Surg. 1997, Mar;84(3):385-8.
29 Van Randen A, Laméris W, van Es HW, van Heesewijk HP, van Ramshorst B, Ten Hove W, et al. A comparison of the Accuracy of Ultrasound and Computed Tomography in common diagnoses causing acute abdominal pain. Eur Radiol. 2011, Jul;21(7):1535-1545.
30 Kaiser AM, Jiang JK, Lake JP, Ault G, Artinyan A, Gonzalez-Ruiz C, et al. The management of complicated diverticulitis and the role of computed tomography. Am J Gastroenterol. 2005, Apr;100(4):910-7.
31 Heverhagen JT, Sitter H, Zielke A, and Klose KJ. Prospective evaluation of the value of magnetic resonance imaging in suspected acute sigmoid diverticulitis. Dis Colon Rectum. 2008, Dec;51(12):1810-5.
32 Alonso S, Pera M, Parés D, Pascual M, Gil MJ, Courtier R, and Grande L. Outpatient treatment of patients with uncomplicated acute diverticulitis. Colorectal Dis. 2010, Oct;12(10 Online):e278-82.
33 Al-Sahaf O, Al-Azawi D, Fauzi MZ, El-Masry S, and Gillen P. Early discharge policy of patients with acute colonic diverticulitis following initial CT scan. Int J Colorectal Dis. 2008, Aug;23(8):817-20.
34 Eglinton T, Nguyen T, Raniga S, Dixon L, Dobbs B, and Frizelle FA. Patterns of recurrence in patients with acute diverticulitis. Br J Surg. 2010, Jun;97(6):952-7.
35 Dutch National Guideline "Diagnostics and treatment of acute diverticulitis of the colon". Dutch National Guideline "Diagnostics and treatment of acute diverticulitis of the colon". 2012
36 Chabok A, Påhlman L, Hjern F, Haapaniemi S, Smedh K, and AVOD Study Group. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg. 2012, Apr;99(4):532-9.
37 Chapman JR, Dozois EJ, Wolff BG, Gullerud RE, and Larson DR. Diverticulitis: a progressive disease? Do multiple recurrences predict less favorable outcomes? Ann Surg. 2006, Jun;243(6):876-830; discussion 880-3.
38 Anaya DA, and Flum DR. Risk of emergency colectomy and colostomy in patients with diverticular disease. Arch Surg. 2005, Jul;140(7):681-5.
39 Ambrosetti P, Chautems R, Soravia C, Peiris-Waser N, and Terrier F. Long-term outcome of mesocolic and pelvic diverticular

abscesses of the left colon: a prospective study of 73 cases. Dis Colon Rectum. 2005, Apr;48(4):787-91.

40 Hamy A, Paineau J, and Société de chirurgie viscérale de l'ouest (SCVO). [Percutaneous drainage of perisigmoid abscesses of diverticular origin]. Ann Chir. 2001, Mar;126(2):133-7.

41 Brandt D, Gervaz P, Durmishi Y, Platon A, Morel P, and Poletti PA. Percutaneous CT scanguided drainage vs. antibiotherapy alone for Hinchey II diverticulitis: a case-control study. Dis Colon Rectum. 2006, Oct;49(10):1533-8.

42 Siewert B, Tye G, Kruskal J, Sosna J, Opelka F, Raptopoulos V, and Goldberg SN. Impact of CT-guided drainage in the treatment of diverticular abscesses: size matters. AJR Am J Roentgenol. 2006, Mar;186(3):680-6.

43 Singh B, May K, Coltart I, Moore NR, and Cunningham C. The long-term results of percutaneous drainage of diverticular abscess. Ann R Coll Surg Engl. 2008, May;90(4):297-301.

44 Bone RC, Grodzin CJ, and Balk RA. Sepsis: a new hypothesis for pathogenesis of the disease process. Chest. 1997, Jul;112(1):235-43.

45 Jimenez MF, Marshall JC, and International Sepsis Forum. Source control in the management of sepsis. Intensive Care Med. 2001;27 Suppl 1S49-62.

46 Salem L, Veenstra DL, Sullivan SD, and Flum DR. The timing of elective colectomy in diverticulitis: a decision analysis. J Am Coll Surg. 2004, Dec;199(6):904-12.

47 Constantinides VA, Heriot A, Remzi F, Darzi A, Senapati A, Fazio VW, and Tekkis PP. Operative strategies for diverticular peritonitis: a decision analysis between primary resection and anastomosis versus Hartmann's procedures. Ann Surg. 2007, Jan;245(1):94-103.

48 Abbas S. Resection and primary anastomosis in acute complicated diverticulitis, a systematic review of the literature. Int J Colorectal Dis. 2007, Apr;22(4):351-7.

49 Alamili M, Gögenur I, and Rosenberg J. Acute complicated diverticulitis managed by laparoscopic lavage. Dis Colon Rectum. 2009, Jul;52(7):1345-9.

50 Toorenvliet BR, Bakker RF, Breslau PJ, Merkus JW, and Hamming JF. Colonic diverticulitis: a prospective analysis of diagnostic accuracy and clinical decision-making. Colorectal Dis. 2010, Mar;12(3):179-86.

51 Rafferty J, Shellito P, Hyman NH, Buie WD, and Standards Committee of American Society of Colon and Rectal Surgeons. Practice parameters for sigmoid diverticulitis. Dis Colon Rectum. 2006, Jul;49(7):939-44.

52 Wong WD, Wexner SD, Lowry A, Vernava A, Burnstein M, Denstman F, et al. Practice parameters for the treatment of sigmoid diverticulitis--supporting documentation. The Standards Task Force. The American Society of Colon and Rectal Surgeons. Dis Colon Rectum. 2000, Mar;43(3):290-7.

53 Andeweg C, Peters J, Bleichrodt R, and van Goor H. Incidence and risk factors of recurrence after surgery for pathology-proven diverticular disease. World J Surg. 2008, Jul;32(7):1501-6.

54 Janes S, Meagher A, and Frizelle FA. Elective surgery after acute diverticulitis. Br J Surg. 2005, Feb;92(2):133-42.

55 Mueller MH, Glatzle J, Kasparek MS, Becker HD, Jehle EC, Zittel TT, and Kreis ME. Long-term outcome of conservative treatment in patients with diverticulitis of the sigmoid

colon. Eur J Gastroenterol Hepatol. 2005, Jun;17(6):649-54.

56 Rafferty J, Shellito P, Hyman NH, Buie WD, and Standards Committee of American Society of Colon and Rectal Surgeons. Practice parameters for sigmoid diverticulitis. Dis Colon Rectum. 2006, Jul;49(7):939-44.

57 Simpson J, Neal KR, Scholefield JH, and Spiller RC. Patterns of pain in diverticular disease and the influence of acute diverticulitis. Eur J Gastroenterol Hepatol. 2003, Sep;15(9):1005-10.

58 Klarenbeek BR, Samuels M, van der Wal MA, van der Peet DL, Meijerink WJ, and Cuesta MA. Indications for elective sigmoid resection in diverticular disease. Ann Surg. 2010, Apr;251(4):670-4.

59 Gervaz P, Inan I, Perneger T, Schiffer E, and Morel P. A prospective, randomized, single-blind comparison of laparoscopic versus open sigmoid colectomy for diverticulitis. Ann Surg. 2010, Jul;252(1):3-8.

60 Tursi A, Brandimarte G, and Daffinà R. Long-term treatment with mesalazine and rifaximin versus rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon. Dig Liver Dis. 2002, Jul;34(7):510-5.

61 Tursi A, Brandimarte G, Elisei W, Giorgetti GM, Inchingolo CD, Danese S, and Aiello F. Assessment and grading of mucosal inflammation in colonic diverticular disease. J Clin Gastroenterol. 2008, Jul;42(6):699-703.

62 Unlü C, Daniels L, Vrouenraets BC, and Boermeester MA. Systematic review of medical therapy to prevent recurrent diverticulitis. Int J Colorectal Dis. 2012, Sep;27(9):1131-6.

63 Alvarado A. A practical score for the early diagnosis of acute appendicitis. Ann Emerg Med. 1986, May;15(5):557-64.

64 Altman DG, and Royston P. What do we mean by validating a prognostic model? Stat Med. 2000, Feb 29;19(4):453-73.

65 Harrell FE, Lee KL, and Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996, Feb 28;15(4):361-87.

66 Justice AC, Covinsky KE, and Berlin JA. Assessing the generalizability of prognostic information. Ann Intern Med. 1999, Mar 16;130(6):515-24.

67 Laméris W, van Randen A, van Gulik TM, Busch OR, Winkelhagen J, Bossuyt PM, et al. A clinical decision rule to establish the diagnosis of acute diverticulitis at the emergency department. Dis Colon Rectum. 2010, Jun;53(6):896-904.

68 Carr AJ, and Higginson IJ. Are quality of life measures patient centred? BMJ. 2001, Jun 2;322(7298):1357-60.

Chapter 2

How to diagnose acute colonic diverticulitis: proposal for a clinical scoring system

Caroline S. Andeweg

Leonike Knobben

Jan C.M. Hendriks

Rob P. Bleichrodt

Harry van Goor

Annals of Surgery 2011 May;253(5):940-6

Abstract

Objective

The aim of this study was to assess and compare the diagnostic value of elements of the disease history, physical examination and routine laboratory tests in patients with suspected acute left-sided colonic diverticulitis (ALCD).

Summary background data

Misdiagnosis rates for diverticulitis vary in literature between 34% and 68% which needs improvement. Because of the frequent misdiagnosis, liberal use of imaging has been recommended. Before making a plea for routine imaging, the diagnostic accuracy of different variables of disease history, physical examination and routine laboratory tests needs to be specified.

Methods

All patients seen on the emergency department because of acute abdominal pain suspected of ALCD in whom an abdominal computed tomography was performed, between January 2002 and March 2006, were studied. Univariate logistic regression was used to study differences in patients' characteristics and symptoms, findings at physical examination and routine laboratory tests between patients with and without ALCD. Independent predictors to the risk of ALCD were identified using multivariate logistic regression and used to create a clinical scoring system.

Results

Of 1290 patients with acute abdominal pain, 287 patients were eligible for analysis. ALCD was the final diagnosis in 124 patients (43%). ALCD was the final diagnosis in 124 patients (43%). Age, one or more previous episodes, localization of symptoms in the lower left abdomen, aggravation of pain on movement, the absence of vomiting, localization of abdominal tenderness in the lower left abdomen and C-reactive protein 50 or more were found to be independent predictors of ALCD. A nomogram was constructed based on these independent predictors with a diagnostic accuracy of 86%.

Conclusions

This study showed that the clinical diagnosis diverticulitis is difficult to make but can be improved using a clinical scoring system. In case of a high chance of ALCD based on the nomogram, additional imaging may not be needed.

Introduction

Colonic diverticular disease affects approximately 35% to 50% of the Western population and increases in prevalence with advancing age.[1] Acute left-sided colonic diverticulitis (ALCD) occurs in 10% to 25% of patients and is a frequently suspected diagnosis in patients presenting with acute abdominal pain.[2] It is a challenge to correctly identify patients with ALCD, because numerous other acute abdominal conditions mimic its clinical picture. A false clinical diagnosis of ALCD may lead to delayed or inadequate treatment, unneeded further investigation, unnecessary and prolonged hospital stay, and increased costs. Unfortunately, clinical evaluation alone seems inadequate and several studies have shown that the clinical diagnosis diverticulitis appears to be wrong in 34% to 68% of cases.[3-5] Because of the frequent misdiagnosis, routine imaging such as computed tomography (CT) and ultrasound (US) has been recommended for patients with a clinical suspicion of diverticulitis with the hope of yielding a rapid and accurate diagnosis.[2] Routine use of imaging techniques, however, has its drawbacks; the ionizing radiation of CT is potentially harmful[6] and US is examiner-dependent.

Decision-making in patients with diverticulitis is a subjective synthesis of clinical information and basic laboratory tests and merely relies on the surgeon's clinical expertise. Similar to acute appendicitis, the diagnostic process in diverticulitis might be improved by using a clinical scoring system. These scoring systems are based on history, physical examination, and routine laboratory tests and are a suitable instrument for identifying patients with a low, intermediate or high chance of having the disease and provide a structured algorithm for further investigation and treatment.[7, 8] The diagnostic value of particular elements of disease history, physical examination and laboratory tests are not well studied for ALCD. A few studies reported on diagnostic features and found the low sensitivity to be the major problem in clinically diagnosing diverticulitis.[9, 10] Up till now there is no report of a scoring system in use for patients suspected of ALCD. The objective of the present study was to assess and compare the diagnostic value of elements of the disease history, physical examination and routine laboratory tests in patients suspected of ALCD and to provide a clinical scoring system that can simply and accurately predict ALCD in clinical practice.

Methods

Between January 2002 and March 2006, routine abdominal CT was done in consecutive adult patients who were hospitalized with acute abdominal pain and who did not require immediate surgery. All patients were seen at the emergency department by junior and senior surgical residents with direct supervision of a surgeon who decided about hospitalization. Patient selection for this study was based on the abdominal CT request forms written in the earlier-mentioned time period. Request forms were reviewed for the

probability of ALCD based on the following specific text: 'suspected diverticulitis' or 'lower left abdominal pain'. Selected forms were crosschecked with the writings of 'clinical suspicion of diverticulitis' in the medical records. Most patients were referred to the emergency department by general practitioners and patients discharged from the emergency department with suspected ALCD but without abdominal CT were not included.

The following data were extracted from the records: gender, age, previous episodes of diverticulitis, duration of symptoms (days), localization of symptoms, aggravation of pain on movement, anorexia, vomiting, signs of illness, localization of abdominal tenderness, rebound tenderness and muscular guarding, body temperature, white blood cell count, C-reactive protein (CRP), and type of treatment.

Computed tomography was used as gold standard for diagnosing ALCD, in case of non-operative management, based on the high sensitivity (94%) and specificity (99%) reported in literature.[11] Pathology and operative reports were used as gold standard in case of operative management. Diverticulitis based on CT was defined if signs of thickening of the colonic wall of 4mm or more was present, with signs of inflammation of the pericolonic fat (hyper vascularisation or pericolic oedema) with or without abscess formation or contained or free perforation.[12] The final diagnosis ALCD was established based on the CT result or the pathology and operative report if applicable. Other diagnoses in case of no diverticulitis on CT, at surgery or in the pathology report, were also noted. In all patients with an alternative diagnosis, the medical record was reviewed for the final diagnosis during follow-up.

Statistical analysis

Analysis was done on complete datasets. Univariate logistic regression was used to study the differences in patients' characteristics and symptoms, findings at physical examination and inflammatory markers between patients with and without documented ALCD. To this purpose, categories of a specific variable were grouped in case of small numbers. The disease prevalences (*n*) and the crude odds ratios (OR) with 95% confidence intervals (CI) are presented. Multivariate logistic regression with selection procedures was used to identify variables that contributed independently to the risk of ALCD. The selection procedures were partitioned into three steps related to the three categories of variables: 1) patients characteristics and symptoms 2) signs at physical examination, and 3) laboratory tests. In each step the selection procedure was performed using variables from that category, while the variables already found were included in the model. The reasoning for this procedure was to find those variables that in addition to those already found in the previous step, significantly contributed to the ability to discriminate patients with ALCD from those without. The adjusted OR with 95% CI of the final model were calculated. The pseudo-R^2 is presented to indicate the information gained by addition of the covariate(s) in the logistic regression model versus a model without any covariates.

The area under the curve (AUC) of the receiver operating characteristic (ROC) curve is used as a measure of predictive discrimination. In general, these measures are too high because the model is developed solely using the study sample and this model will perform less on a different random sample. Therefore, to evaluate the reliability of the created prediction model, an internal validation was performed using bootstrap methods and the corrected R^2 and the corrected AUC are presented.[13] Using the multivariate prognostic model, a boundary value (i.e., the optimal cut-off point) of the risk of ALCD, given the values of the prognostic variables only, was constructed under the condition of equal 'costs' of misclassification of cases and non-cases. Finally, a nomogram was constructed using the multivariable prognostic model. Such a nomogram can be used by filling in the values of each of the independent risk factors separately. The corresponding number of points is then read from the scale mentioned earlier. These are then summed to give a total point score, which is translated into a probability of having ALCD by using the two scales at the bottom of the nomogram. All statistical analyses were performed using SAS version 8.2, and the nomogram was constructed using standard procedures in R version 2.6.1.

Results

One thousand two hundred ninety consecutive admitted patients with acute abdominal pain had an abdominal CT scan. Three hundred seven patients (24%) fulfilled the inclusion criteria of suspected ALCD based on the CT request forms and the crosscheck with the medical records. The records of twenty patients (7%) were incomplete and excluded for analysis. A total of 287 patients (110 men and 177 women) remained for further analysis of which 124 patients (43%) were diagnosed with ALCD as the final diagnosis (*Figure 1*).

Table 1 summarizes the final diagnoses based on CT findings and the clinical picture. Main diagnoses in the remaining 163 patients included no abnormalities, gynaecologic disorders, and diverticulosis without inflammation. All patients were followed for at least six months after the initial diagnosis and none of these patients developed ALCD; that is, there were no false negatives. Thirty-one patients (25%) required surgery, with the majority of them (77%) having a first episode of ALCD. Perioperative findings and pathology reports confirmed the diagnosis ALCD in all patients and no additional disorders were found during surgery or in the pathology reports.

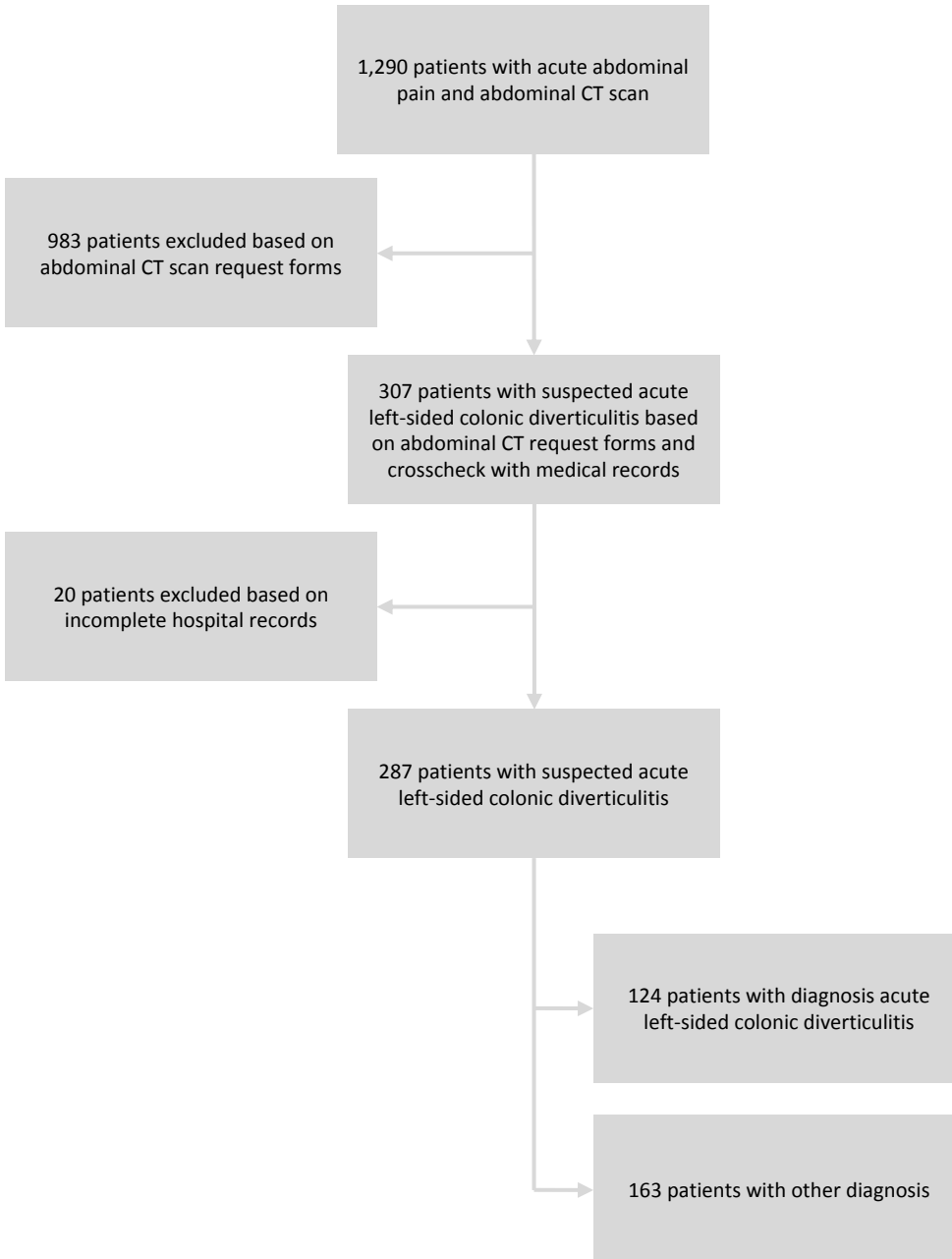


Figure 1: Flowchart of the selection process for the study group

Table 1: Alternative diagnoses in patients suspected of having acute left-sided colonic diverticulitis (ALCD) based on initial CT scan findings and subsequent clinical diagnosis

Diagnosis	***N* patients**
No abnormalities found	57
Gynecologic abnormalities	15
Other	15
Diverticulosis coli without infection	13
Colorectal malignancy	11
Renal abnormalities	10
Ischemic colitis	9
Enteritis	9
Intestinal obstruction	7
Appendicitis acuta	4
Mesenteric lymphadenitis	3
Psoas hematoma	2
Sigmoid volvulus	2
Cholecystitis	2
Iliacal aneurysm	2
Femoral hernia	1
Epiploic appendagitis	1
Total	163

Baseline patient characteristics and symptoms expressed by crude odds ratios for the probability of ALCD using univariate analysis are given in *Table 2*. Statistically significant predictors of ALCD were age (>50 years, OR 3.99, CI: 1.99-8.03), one or more previous episodes of diverticulitis (OR 7.60, CI: 3.72-15.52), localization of symptoms in the lower left abdomen (OR 3.43, CI: 1.98-5.92) and aggravation of pain on movement (OR 2.97, CI: 1.83-4.83). Vomiting was a negative predictor of ALCD (OR 0.49, CI: 0.59-0.86). The discriminating power of the patients' characteristics and symptoms expressed as AUC of the ROC curve was low (0.52-0.64), except for the variable localization of pain (AUC = 0.73).

The diagnostic value of physical examination expressed by crude odds ratios for the probability of ALCD is given in *Table 3*. Localization of abdominal tenderness in the lower left abdomen (OR 5.36, CI: 3.18-9.04), rebound tenderness (OR 2.92, CI: 1.80-4.74) and body temperature ≥38.5 (OR 2.00, CI: 1.06-3.78) were statistical significant predictors of ALCD. Discriminating power of these variables was comparable to the discriminating power of the patient characteristics and symptoms with an AUC of 0.51-0.63 and thus generally low. Abdominal tenderness on physical examination was the only variable with a relatively high discriminating power (AUC = 0.70).

Table 2: The number of patients with baseline characteristics and symptoms and the odds ratios with 95% confidence interval for the probability of acute left-sided colonic diverticulitis, using univariate logistic regression

Characteristic		Number of patients		OR (95% CI)	AUC (%) (95% CI)
		ALCD + (*n*=124)	ALCD – (*n*=163)		
Gender	Male	50	60	1.16 (0.72; 1.87)	52
	Female	74	103	1.00 (reference)	(46-58)
Age (years)	<40	12	45	1.00 (reference)	62
	41-70	87	88	2.08 (0.85; 5.11)	(57-67)
	≥71	25	30	3.99 (1.99; 8.03)	
Previous episodes	No	80	153	1.00 (reference)	64
	One or more	44	10	7.60 (3.72; 15.52)	(59-69)
Duration of symptoms (days)	0-1	48	60	1.00 (reference)	57
	2-3	47	80	0.73 (0.44; 1.24)	(51-64)
	≥4	29	23	1.58 (0.81; 3.07)	
Localization of symptoms (abdomen)	Lower left	81	44	3.43 (1.98; 5.92)	73
	Lower right	7	52	0.25 (0.11; 0.61)	(67-78)
	Diffuse	36	67	1.00 (reference)	
Aggravation of pain on movement	No	51	110	1.00 (reference)	63
	Yes	73	53	2.97 (1.83; 4.83)	(57-69)
Anorexia	No	62	68	1.00 (reference)	54
	Yes	62	95	0.71 (0.44; 1.13)	(48-60)
Vomiting	No	99	108	1.00 (reference)	57
	Yes	25	55	0.49 (0.59; 0.86)	(51-62)
Diarrhea	No	95	133	1.00 (reference)	52
	Yes	29	30	1.35 (0.76-2.40)	(48-57)

ALCD + indicates patients with acute left-sided colonic diverticulitis; ALCD – indicates patients without acute left-sided colonic diverticulitis; OR: Odds Ratio; CI: Confidence Interval; AUC: Area Under the ROC Curve

Table 3: Number of patients with a diagnostic value of physical examination and the odds ratios with 95% confidence interval for the probability of acute left-sided colonic diverticulitis, using univariate logistic regression

Characteristic		Number of patients		OR (95% CI)	AUC (%) (95% CI)
		ALCD + (*n*=124)	ALCD – (*n*=163)		
Signs of illness	No	55	79	1.00 (reference)	52
	Yes	69	84	1.18 (0.74; 1.89)	(46-58)
Localization of abdominal tenderness	Lower left	94	57	5.36 (3.18; 9.04)	70
	Other[†]	30	106	1.00 (reference)	(64-75)
Rebound tenderness	No	49	107	1.00 (reference)	63
	Yes	75	56	2.92 (1.80; 4.74)	(57-69)
Body temperature (degrees Celsius)	≤37.5	49	79	1.00 (reference)	57
	37.6-37.9	22	32	1.11 (0.58; 2.12)	(50-63)
	38.0-38.4	22	27	1.31 (0.68; 2.56)	
	≥38.5	31	25	2.00 (1.06; 3.78)	

[†] Group contains patients with right-sided and diffuse abdominal tenderness

ALCD + indicates patients with acute left-sided colonic diverticulitis; ALCD – indicates patients without acute left-sided colonic diverticulitis; OR: Odds Ratio; CI: Confidence Interval; AUC: Area Under the ROC Curve

Diagnostic value of laboratory tests expressed by crude OR for the probability of ALCD is given in *Table 4*. An elevated white blood cell count and a CRP level 50mg/l or more (OR 3.78, CI: 1.92-7.43) were statistically significant predictors of ALCD. The discriminating power of each laboratory test was low (AUC = 0.61-0.63).

Table 4: Number of patients with a diagnostic value of laboratory tests and the odds ratios with 95% confidence interval for the probability of acute left-sided colonic diverticulitis, using univariate logistic regression

Characteristic		Number of patients		OR (95% CI)	AUC (%) (95% CI)
		ALCD + (*n*=124)	ALCD – (*n*=163)		
WBCC	<10	35	77	1.00 (reference)	61
($x10^9$/l)	10-12	31	27	2.53 (1.32; 4.85)	
	13-15	29	26	2.45 (1.26; 4.76)	
	>15	29	33	1.93 (1.02; 3.66)	
CRP	≤10	14	46	1.00 (reference)	63
(<10mg/l)	11-49	26	44	1.94 (0.90; 4.19)	
	≥50	84	73	3.78 (1.92; 7.43)	

ALCD + indicates patients with acute left-sided colonic diverticulitis; ALCD – indicates patients without acute left-sided colonic diverticulitis; OR: Odds Ratio; CI: Confidence Interval; AUC: Area Under the ROC Curve; WBCC: White Blood Cell Count (4.3-10.0 $x10^9$/l); CRP: C-reactive protein (<10mg/l)

Table 5 shows the adjusted OR using a multivariate logistic regression model with selection procedures. Age more than 50 years, one or more previous episodes, localization of symptoms in the lower left abdomen, aggravation of pain on movement, the absence of vomiting, localization of abdominal tenderness in the lower left abdomen and CRP 50 or more were found to be independent predictors of ALCD. The area under the ROC curve as a measure of predictive discrimination for this model was 86% (95% CI: 82%-91%) and the pseudo-R^2 was 50%. After bootstrapping the corrected AUC and the corrected R^2 were, 84% and 44%, respectively.

A nomogram (*Figure 2*) was constructed to calculate the probability of ALCD in patients with suspicion of ALCD. *Figure 3* shows the accompanying confidence intervals of the estimated probability of ALCD calculated from the nomogram. A probability of ALCD greater than 50% had a corresponding sensitivity and specificity of 75% and 84%, respectively. For example, a patient 55 years of age (= 40 points) with one previous episode of diverticulitis (= 88 points), with lower left abdominal tenderness (= 57 points), with a CRP of 66 (= 85 points), with localization of symptoms in the lower left abdomen (= 100 points), without aggravation of pain on movement (= 0 points) and without vomiting (= 50 points) will receive a total of 420 points. The probability for having ACLD is then 93%, or 2.7 on the linear prediction scale, with a CI of 84%-98% (*Figure 3*).

Table 5: The adjusted odds ratios with 95% confidence interval for the probability of acute left-sided colonic diverticulitis, using multivariate logistic regression analysis with selection procedures.*

Variable		Adjusted OR (95% CI)
Age (years)	<50	1.00 (reference)
	≥50	2.15 (1.05; 4.37)
Previous episodes	No	1.00 (reference)
	One or more	5.67 (2.36; 13.62)
Localization of symptoms	Lower left	1.73 (0.80; 3.74)
	Lower right	0.26 (0.09; 0.73)
	Diffuse	1.00 (reference)
Aggravation of pain on movement	No	1.00 (reference)
	Yes	3.28 (1.71; 6.63)
Vomiting	No	1.00 (reference)
	Yes	0.38 (0.17; 0.79)
Localization of abdominal tenderness	Lower left	2.96 (1.35; 6.49)
	Other†	1.00 (reference)
CRP (<10mg/l)	≤10	1.00 (reference)
	11-49	1.96 (0.73; 5.24)
	≥50	5.18 (2.11; 12.76)

* The area under the ROC curve was 86% (95% CI: 82%-91%)
† Group contains patients with right-sided and diffuse abdominal tenderness

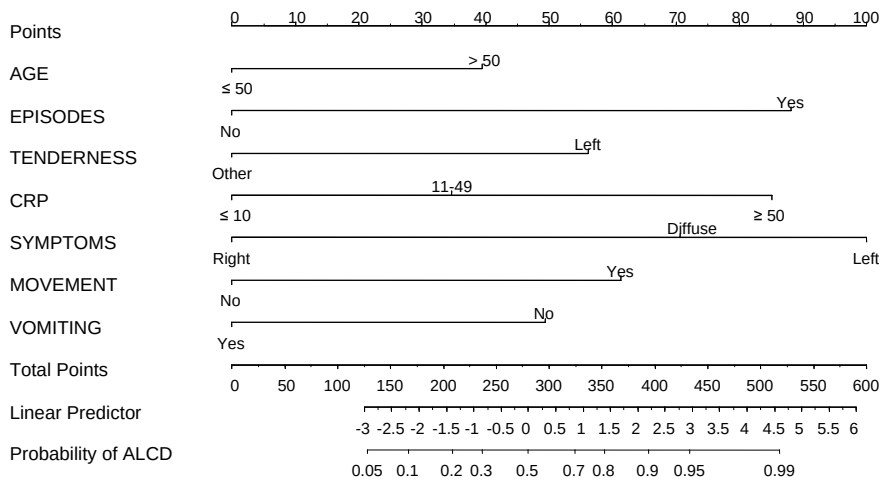


Figure 2: Nomogram to calculate the risk of acute left-sided diverticulitis (ALCD) in patients suspected of ALCD. Draw a vertical line for all the variables to the 'Points' axis on the top of the page. Sum the points for each variable and locate this on the 'Total Points' axis at the bottom of the page. Draw a vertical line from this spot on the 'Total Points' axis straight down to calculate the risk of ALCD. Age in years; Episodes: one or more previous episodes of diverticulitis; Tenderness: localization of pain by disease history, Left: pain lower left abdomen. Other: pain lower right abdomen and diffuse abdominal pain; CRP in mg/l; Symptoms**:** localization of pain by physical examination; Left: pain lower left abdomen; Diffuse: diffuse abdominal pain and Right: right-sided abdominal pain; Movement: aggravation of pain on movement.

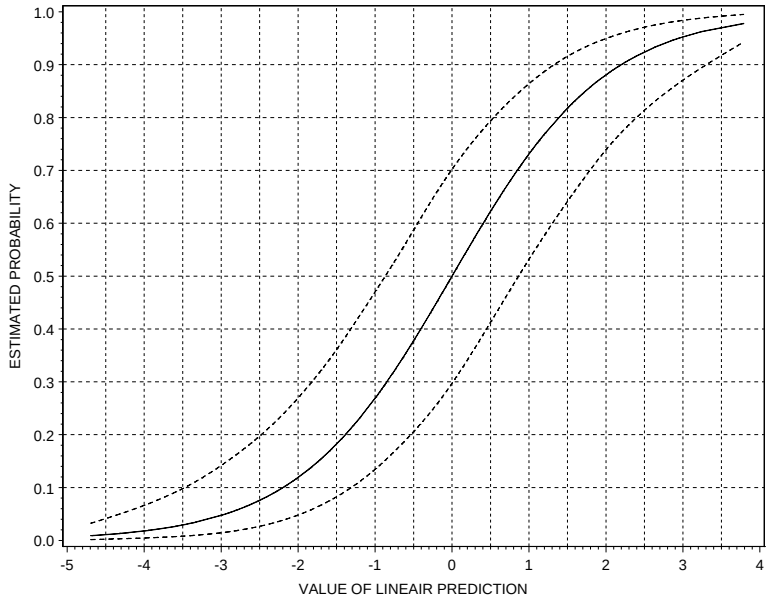


Figure 3: The estimated probability of acute left-sided colonic diverticulitis (solid line) and the 95% confidence bands (broken lines) against the linear predictor. The 95% confidence interval is found by means of the vertical intersection with the broken lines at the point where the estimated probability intersects the solid line. For example the 95% CI of an estimated probability of 0.5 is (0.3-0.7).

Discussion

In this study, the majority of patients were misdiagnosed based on clinical evaluation alone. To improve clinical decision making, we studied the diagnostic value of 15 elements of the disease history, physical examination and laboratory tests in patients suspected of ALCD. The discriminating power of the different variables was generally low. Age, a previous episode of diverticulitis, tenderness in the lower left abdomen both as complaint and at physical examination, aggravation of pain on movement, CRP 50 or more and the absence of vomiting were found to be independent predictors of ALCD. A nomogram was built based on these variables with good diagnostic accuracy. Using this nomogram the probability of ALCD can be simply and reliably predicted in clinical practice.

We selected patients with suspected ALCD in a large group of patients seen at the emergency department and admitted with acute abdominal pain. All patients underwent abdominal CT scan, which allowed us to differentiate between patients with and without suspected ALCD. The approach to match clinical findings in a large consecutive group of patients with CT outcome as gold standard has strengthened our results. Patient selection based on CT request forms, on the contrary, harbors a few limitations which should be

taken into account before generalizing our results. Most of our patients were referred to the emergency department by a general practitioner. Referral patterns differ between countries, resulting in differences in disease prevalence and patient population. A number of patients with suspected ALCD will be treated by the general practitioner and not referred to the emergency department, hence missed in our analysis. Also patients with minimal abdominal pain and no general signs of illness that are discharged from the emergency department without imaging and patients with acute abdominal pain in need for urgent surgery were not included in our analysis. There is a great variation in the intensity of symptoms at presentation of patients with suspected diverticulitis. Some patients can be treated on an outpatient basis where as others require hospitalization and medical treatment or surgery. The results of this study reflect a patient population with abdominal pain seen on the emergency department in a large University Hospital and apply to patients with suspected diverticulitis needing hospital admission.

In our study clinical suspicion proved to be correct in only 43% of patients, demonstrating that the majority of patients were misdiagnosed on the basis of clinical decision making alone. Only two prospective studies report on diagnostic accuracy in colonic diverticulitis and correctly identified 64% and 68% of patients with diverticulitis based on clinical parameters alone.[9, 10] Our misdiagnosis rate was higher compared to these two studies but is in accordance with previously published data of reported misdiagnosis rates varying between 34% and 68%.[3, 5, 14]

In our study, overestimation of the number of patients with suspected ALCD might have occurred because doctors tend to write down a differential diagnosis on the CT request forms including ALCD. To minimize this problem, we crosschecked the medical records and found that all 287 patients were hospitalized with the entrance diagnosis ALCD. Diagnostic accuracy depends on the surgeon's previous experience and should always be taken into account when interpreting clinical findings. In our study all patients were seen by junior- and senior residents but always supervised by an experienced surgeon. This approach minimizes the risk of lack of experience being the cause of a high misdiagnosis rate. Based on our findings, it seems to be a safe assumption that misdiagnosis rates in patients with suspected diverticulitis truly are high.

Because of the high clinical misdiagnosis rates and the possibility that other diseases mimicking ALCD are missed, the view nowadays is that imaging is mandatory in the initial assessment of patients suspected of ALCD.[2, 15] Ultrasound and CT are used in daily practice to complement clinical assessment and physical examination in diagnosing ALCD. The main disadvantages in case of US are operator-dependent factors and the emergence of inconclusive results that lead to further uncertainty in clinical decision making. Furthermore, US performs less in patients with high amounts of body fat.[16] The main disadvantages of CT are that it requires ionizing radiation with a potential cancer risk and the use of intravenous contrast material.[6] Although the disadvantages of additional

imaging are well known, little has been done to improve clinical decision making without the use of additional imaging techniques.

This is the first study in which the diagnostic value of the different elements of disease history, physical examination and laboratory tests is analyzed for their contribution to the prediction of ALCD. Seven independent predictors for ALCD were found, by which variables of disease history and patient characteristics were the most contributing. Age, a previous episode of diverticulitis, tenderness in the lower left abdomen as complaint and at physical examination, aggravation of pain on movement, CRP 50 or more and the absence of vomiting were the most important clinical parameters to consider when differentiating ALCD from other acute abdominal conditions. Most of the individual variables alone did not have high discriminating power, but when combined, the discriminating power of the independent risk factors was improved to 86%. To use this finding in clinical practice the individual risk factors were translated into a nomogram. This nomogram can be used as a clinical scoring system that estimates the probability of ALCD in patients who are seen at the emergency department with acute abdominal pain and a clinical suspicion of ALCD. Accuracy of such a nomogram represents the most important consideration. To assess our model's predictive accuracy we used the area under the ROC curve. Generally accepted accuracy ranges of a model are 70% to 80%.[17] Even though our model can be considered a good prediction model (accuracy of 86% and 84% after internal validation), validation of the model and the proposed diagnostic algorithm in a different patient population is an important next research step.

The optimal sensitivity and specificity of the ROC curve in our study were 77% and 85%, respectively. The specificity of our model can compete with that of US (90%), as found in a recent meta-analysis.[11] Specificity of CT in this study was higher (99%), but did not significantly differ from US. Sensitivity of US and CT reached 92% and 94%, respectively, in the meta-analysis as compared with 77% of the nomogram. It should be realized that these sensitivities and specificities come from meta-analyses having included the best available evidence. Sensitivity of our model is expectedly lower than that of additional imaging, but still far better than based on clinical assessment alone. The big advantage of CT, over US or the nomogram, is the better identification of alternative diagnoses and CT better demonstrates the extent of the disease in case of complicated diverticulitis. Our model provides an accurate prediction of the chance of having ALCD but in case of a low chance of ALCD the model cannot predict which other disease is present. On the contrary, in case of a high chance of ALCD based on the nomogram, additional imaging may not be needed. The nomogram can be of help in determining the risk of ALCD and the decision for further investigation and treatment.

This study showed that the clinical diagnosis diverticulitis is difficult to make but can be improved by the use of a clinical scoring system. Elements of disease history, physical examination and laboratory tests provide important diagnostic information and when put

into a nomogram a reliable prediction can be made of the chance of having ALCD. These variables should therefore be included in the diagnostics workup and integrated into the clinical assessment of patients suspected of having acute colonic diverticulitis. In case of a high chance of ALCD based on the nomogram, additional imaging may not be needed.

Reference list

1 Painter NS, Burkitt DP. Diverticular disease of the colon: a deficiency disease of Western civilization. Br Med J 1971; 2:450-454.

2 Rafferty J, Shellito P, Hyman NH, Buie WD. Practice parameters for sigmoid diverticulitis. Dis Colon Rectum 2006; 49:939-944.

3 Wexner SD, Dailey TH. The initial management of left lower quadrant peritonitis. Dis Colon Rectum 1986; 29:635-638.

4 Cho KC, Morehouse HT, Alterman DD, Thornhill BA. Sigmoid diverticulitis: diagnostic role of CT--comparison with barium enema studies. Radiology 1990; 176:111-115.

5 Farag SM, Wustner M, Sturm J, Werner A, Diehl SJ, Duber C, Post S. [Primary diagnostics of acute diverticulitis of the sigmoid]. Ultraschall Med 2004; 25:342-347.

6 Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med 2007; 357:2277-2284.

7 Andersson M, Andersson RE. The appendicitis inflammatory response score: a tool for the diagnosis of acute appendicitis that outperforms the Alvarado score. World J Surg 2008; 32:1843-1849.

8 Alvarado A. A practical score for the early diagnosis of acute appendicitis. Ann Emerg Med 1986; 15:557-564.

9 Laurell H, Hansson LE, Gunnarsson U. Acute diverticulitis--clinical presentation and differential diagnostics. Colorectal Dis 2007; 9:496-501.

10 Toorenvliet BR, Bakker RF, Breslau PJ, Merkus JW, Hamming JF. Colonic diverticulitis: a prospective analysis of diagnostic accuracy and clinical decision making. Colorectal Dis 2009.

11 Lameris W, van Randen A, Bipat S, Bossuyt PM, Boermeester MA, Stoker J. Graded compression ultrasonography and computed tomography in acute colonic diverticulitis: meta-analysis of test accuracy. Eur Radiol 2008; 18:2498-2511.

12 Werner A, Diehl SJ, Farag-Soliman M, Duber C. Multi-slice spiral CT in routine diagnosis of suspected acute left-sided colonic diverticulitis: a prospective study of 120 patients. Eur Radiol 2003; 13:2596-2603.

13 F.E.Harrel jrSVNYI2. Regression modeling strategies: with applications to linear models, logistic regression and survival analysis. 2009.

14. Pradel JA, Adell JF, Taourel P, Djafari M, Monnin-Delhom E, Bruel JM. Acute colonic diverticulitis: prospective comparative evaluation with US and CT. Radiology 1997; 205:503-512.

15 Balfe DM, Levine MS, Ralls PW, Bree RL, DiSantis DJ, Glick SN, Megibow AJ, Saini S, Shuman WP, Greene FL, Laine LA, Lillemoe K. Evaluation of left lower quadrant pain. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000; 215 Suppl:167-171.

16 Liljegren G, Chabok A, Wickbom M, Smedh K, Nilsson K. Acute colonic diverticulitis: a systematic review of diagnostic accuracy. Colorectal Dis 2007; 9:480-488.

17 Chun FK, Karakiewicz PI, Briganti A, Walz J, Kattan MW, Huland H, Graefen M. A critical appraisal of logistic regression-based nomograms, artificial neural networks, classification and regression-tree models, look-up tables and risk-group stratification models for prostate cancer. BJU Int 2007; 99:794-800.

Letter to the Editor:

The role of abdominal imaging in cases with a high probability of acute left-sided colonic diverticulitis based on a clinical scoring system

Andeweg, et al.[1] have proposed a clinical scoring system for the diagnosis of acute left-sided colonic diverticulitis (ALCD), which was shown to improve clinical diagnosis rates with the help of a nomogram. This is undoubtedly a useful clinical tool expected to reduce misdiagnosis rates for diverticulitis after further validation in prospective studies. We would like, however, to point out two significant limitations of this study.

First, the authors have expectedly identified the history of previous episodes of diverticulitis as an independent predictor of the risk of ALCD, with the highest odds ratio in multivariate logistic regression analysis. However, a positive or negative history of left-sided diverticular disease without signs of diverticulitis has not been included in their analysis. With the increasing use of colonoscopy as a screening tool for colorectal cancer above the age of 50 years and given that diverticulosis and diverticulitis are associated with advanced age, more patients are expected to be aware of the presence or absence of asymptomatic diverticular disease. A positive history of left-sided diverticulosis may facilitate clinical differentiation in cases of suspect clinical presentation, whereas a negative history in a recent lower endoscopy may strongly influence clinical diagnosis against diverticulitis. In our opinion, history of asymptomatic left-sided diverticular disease should have been included in multivariate analysis and probably in the construction of this useful nomogram in case of an associated high diagnostic value.

Second, the authors have stressed the use of their clinical scoring system as a clinical adjunct to diagnose ALCD, but also as an approach to restrict the use of additional imaging, i.e. ultrasound and abdominal computed tomography (CT), in selected cases with high probability of ALCD as calculated by linear prediction. Although their clinical scoring system bears relatively high sensitivity and specificity rates, a more thorough assessment of its utility in clinical decision-making might, interestingly, reveal an enhanced role for CT imaging. Imaging with abdominal CT upon admission for ALCD has been so far strongly recommended[2] to demonstrate the severity, the local extent of the disease and the presence of possible complications with the exception of patients presenting with diffuse peritonitis. The authors suggest that additional imaging may not be needed in cases with a high chance of ALCD based on the nomogram. However, abdominal imaging provides significant information for the management of these patients through classification in appropriate treatment groups, i.e. conservative therapy vs. percutaneous drainage of a pericolic abscess vs. surgery,[3] and affects the duration and cost of hospitalization. Moreover, the severity of ALCD on CT imaging has been previously shown to be predictive of the risk of nonoperative treatment failure and secondary long-term complications after the initial episode.[4, 5] In fact, patients with a high probability of ALCD constitute a group

which will mostly benefit from abdominal CT from a clinical aspect, ensuring that they will receive the most appropriate treatment. Therefore, we believe that the nomogram presented in this study could be really useful for the selection of patients who actually need additional imaging between those that present with acute abdominal pain and suspect ALCD in the emergency department. In other words, the diagnosis of ALCD in a case with high probability based on the nomogram should be documented and further investigated with abdominal CT. However, a valuable clinical tool has emerged from this study and we would like to compliment the authors for their contribution in a clinical condition with high misdiagnosis rates.

Nikolaos P. Karidis, MD
Dimitrios Dimitroulis, PhD
Gregory Kouraklis, PhD
Second Department of Propedeutic Surgery, Medical School, University of Athens, Greece

References

1 Andeweg CS, Knobben L, Hendriks JC, et al. How to Diagnose Acute Left-sided Colonic Diverticulitis: Proposal for a Clinical Scoring System. Ann Surg. 2011; 253(5):940-6.

2 Rafferty J, Shellito P, Hyman NH, et al. Practice parameters for sigmoid diverticulitis. Dis Colon Rectum. 2006; 49(7):939-44.

3 Ambrosetti P, Becker C, Terrier F. Colonic diverticulitis: impact of imaging on surgical management -- a prospective study of 542 patients. Eur Radiol. 2002; 12(5):1145-9.

4 Kaiser AM, Jiang JK, Lake JP, et al. The management of complicated diverticulitis and the role of computed tomography. Am J Gastroenterol. 2005; 100(4):910-7.

5 Ambrosetti P. Acute diverticulitis of the left colon: value of the initial CT and timing of elective colectomy. J Gastrointest Surg. 2008; 12(8):1318-20.

Reply

We are pleased to have the opportunity to respond to the letter to the editor and would like to thank Dr. Karidis and his colleagues for the interest in our work. The nomogram was developed based on the scientific question whether or not the clinical diagnosis acute colonic left-sided diverticulitis (ALCD) could be improved by the use of a scoring system, similar to the way clinical scoring systems have been developed to diagnose acute appendicitis. Based on the nomogram we aim to develop a structured algorithm for further investigation and treatment of patients with ALCD, and therefore we highly appreciate to exchange views with other experts in the field on how we could improve the nomogram and thereby the work-up of patients with ALCD.

The authors suggest including the presence or absence of asymptomatic diverticular disease in the multivariate analysis and in case of an associated high diagnostic value to use this in the nomogram. This suggestion has merit because a patient needs to have diverticulosis to develop diverticulitis and in literature, an estimated 10-25% risk of diverticulitis in patients with asymptomatic diverticulosis has been reported. However, the suggestion of the authors raises the question how to establish asymptomatic diverticular disease, e.g., when a patient has no complaints. Routine screening colonoscopy for this diagnosis is not done and screening for (pre)malignancies has only recently started in The Netherlands and many other countries. Including absence or presence of asymptomatic diverticulosis in the nomogram will imply blank spots in a considerable amount of patients. We also believe that the presence or absence of asymptomatic diverticulosis is already partly reflected in the variable age, being an independent predictor of ALCD in our study. Asymptomatic diverticulosis increases with age and is estimated less than 10% in young patients (<40 years) and increases to 65-70% in patients above 65 years of age.[1] As a result, the risk of developing ALCD will increase with advancing age, as confirmed in our study; a four times higher risk of developing ALCD in the group of patients older than 50 years of age. We could safely assume that with advancing age the risk of asymptomatic diverticulosis and the risk of developing ALCD will increase.

The authors also advocate a more prominent role of CT imaging in case of a high likelihood of ALCD based on the clinical scoring system. Although CT imaging plays a major role in staging the severity of the disease and may even be predictive of the risk of nonoperative treatment failure and secondary long-term complications after the initial episode, in most patients with first or recurrent episodes of ALCD the disease will run a benign course. These patients, if diagnosed with a high degree of probability based on the nomogram are not expected to gain from additional imaging and can be withheld, in our opinion, from additional imaging from a diagnostic point of view. Moreover, the latest insight on the natural history of diverticulitis has shown that most perforations do not occur after recurrences, but at the first attack of diverticulitis. In case of suspected complicated ALCD, a CT scan is indicated to adequately stage the severity of the disease and to initiate proper

treatment and to classify patients in appropriate treatment groups, i.e., conservative therapy versus percutaneous drainage of abscesses or surgery.

Finally, we would like to mention the external validation study in which the nomogram was validated in another Dutch database provided by Laméris et al. They prospectively enrolled 1021 consecutive patients presenting at the Emergency Department with acute abdominal pain and found similar variables that have the best predictive value in diagnosing ALCD. Based on the variables with the highest discriminating power they developed a clinical decision rule.[4] Both predictive tools were used crosswise for external validation and in addition were validated in a third independent cohort provided by Laurell et al.[5] Despite the fact that the two recent predictive tools have been developed independently, both analyses ended up with the same variables that have the best predictive value in diagnosing acute ALCD. Preliminary results of this unpublished study showed that isolated left tenderness in the lower left abdomen, CRP >50 and the absence of vomiting have significant predictive value in patients with suspected ALCD. With additional variables present (older age, pain on movement, previous episodes of diverticulitis) the certainty of the diagnosis can be increased. Hopefully, the combination of these variables will proof to be useful in limiting the use of CT imaging to diagnose ALCD. A future study prospectively evaluating patients with acute abdominal pain subjected to the externally validated nomogram, will give more insight in the use of these variables in reducing the use of abdominal CT imaging to diagnose diverticulitis. It might be worthwhile to introduce asymptomatic diverticulitis as a covariate in this study.

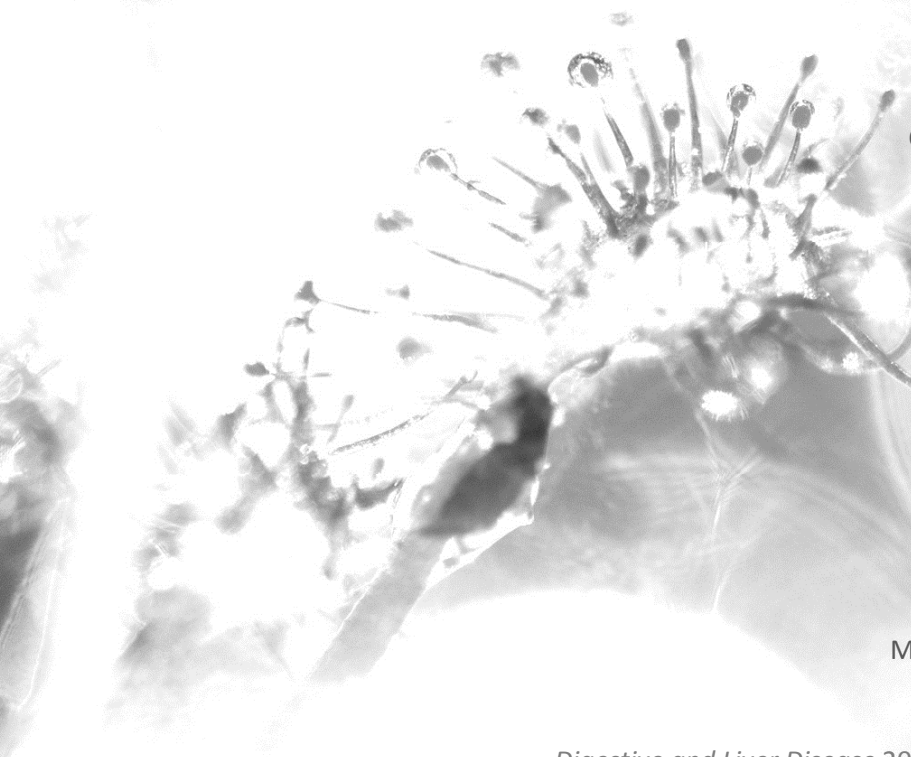
Caroline S. Andeweg, MD
Robert P. Bleichrodt, MD
Harry van Goor, MD
Department of Surgery, Radboud University Nijmegen Medical Centre, The Netherlands

References

1 Stollmann N, Raskin JB. Diverticular disease of the colon. Lancet 2004; 363:631-639.
2 Salem TA, Molloy RG, O'Dwyer PJ. Prospective, five-year follow-up study of patients with symptomatic uncomplicated diverticular disease. Dis Colon Rectum 2007; 50:1460-1464.
3 Chapman J, Davies M, Wolff B et al. Complicated diverticulitis: is it time to rethink the rules? Ann Surg 2005; 242:576-581.
4 Laméris W, van Randen A, van Gulik TM et al. A clinical decision rule to establish the diagnosis of acute diverticulitis at the emergency department. Dis Colon Rectum 2010; 53(6):896-904.
5 Laurell H, Hansson LE, Gunnarsson U. Acute diverticulitis—clinical presentation and differential diagnostics. Colorectal Dis 2007; 9:496-501.

Chapter 3

External validation of two tools for the clinical diagnosis of acute diverticulitis without imaging



Jordy S. Kiewiet

Caroline S. Andeweg

Helena Laurell

Lidwine Daniels

Wytze Laméris

J.B. Reitsma

Jan C.M. Hendriks

Robert P. Bleichrodt

Harry van Goor

Marja A. Boermeester

Digestive and Liver Disease 2014 Feb;46(2):119-24

Abstract

Aim

The aim of this study was external of the validation and comparison diagnostic accuracy of two predictive tools, the emergency department triad and the clinical scoring tool in diagnosing acute diverticulitis.

Methods

The two derivation datasets were used crosswise for external validation. In addition, both tools were validated in a third independent cohort. Predictive values were reassessed and the Area Under the Curve expressed discriminatory capacity. Performance was compared by calculating positive predictive values of the emergency department triad in the validation cohorts and with a cut-off analysis for the clinical scoring tool at a positive predictive value of 90%.

Results

Predictive value of the emergency department triad was comparable to the clinical scoring tool. The positive predictive value of the emergency department triad (97%) decreased in the clinical scoring tool cohort (81%) and was excellent in the independent cohort (100%), identifying 24%, 20% and 14% of the patients. A smaller proportion of patients with diverticulitis could be identified with the clinical scoring tool (6%, 19% and 9%).

Conclusion

The emergency department triad as well as the clinical scoring tool has significant predictive value in external cohorts of patients suspected of diverticulitis. These tools can be used to select patients in whom additional imaging to diagnose acute diverticulitis may be omitted.

Introduction

Acute colonic diverticulitis is a frequently encountered diagnosis in patients presenting at the Emergency Department (ED) with acute abdominal pain.[1, 2] Early distinction from other diagnoses is of great value since treatment of acute diverticulitis is conservative in the majority of cases. Hence, adequate and timely diagnosis could prevent needless additional imaging or hospitalization and therefore costs, but most of all reduce the burden on the patient. Although stated in guidelines that the diagnosis often can be made by clinical evaluation[2], additional diagnostic imaging is widely used in patients with suspected acute diverticulitis.[3, 4] Several studies endorse the feeling of clinicians that the current clinical evaluation is not adequate, expressed in wrongful diagnosis of diverticulitis of up to 40%.[5, 6]

Two recent studies, published almost simultaneously, developed a predictive tool that can increase the diagnostic accuracy and reliability of the clinical diagnosis of acute colonic diverticulitis. Both predictive tools increase the diagnostic accuracy of the clinical evaluation. Laméris et al. constructed a decisional rule consisting of three questions.[1] These questions address elements of disease history, physical examination and laboratory tests. The aim of this decisional triad is to have a high diagnostic accuracy for patients suspected of diverticulitis and rule out those with other causes of acute abdominal pain. Andeweg et al. used a slightly different approach and looked at the diagnostic value of a variety of elements of disease history, physical examination and laboratory tests.[7] Herewith, a scoring system has been constructed that attributes points to the separate elements of clinical evaluation that are independent predictors resulting in a probability of having acute diverticulitis. Before any predictive tool, be it a scoring system or a decisional rule, can be propagated for widespread use it should be tested in other data sets than it was developed in, also known as external validation.[8-12] External validation enhances the general applicability and can address historical, geographic and methodological differences.[10] External validation of these two recently developed predictive tools may further increase the diagnostic accuracy of the clinical diagnosis of acute diverticulitis and minimizes unnecessary imaging.

Therefore, the aim of this study was external validation and comparison of the diagnostic accuracy of the decisional rule and the scoring system. If one of these tools or both perform well in external validation it becomes possible to minimize unnecessary imaging to diagnose diverticulitis and thereby reduce patient burden and healthcare utilization.

Material and methods

Data

Laméris et al. prospectively enrolled consecutive patients with acute abdominal pain presenting at the Emergency Department (ED) in a multicenter diagnostic accuracy study between March 2005 and November 2006.[1, 13] With this dataset the 'ED triad' was constructed to diagnose patients with acute diverticulitis. Only patients in whom additional imaging was deemed necessary after clinical evaluation were included and these patients received a full diagnostic protocol (plain X-ray, ultrasound and CT). For the development of the ED triad, patients were selected from the study cohort when patients were suspected of having acute diverticulitis.

Andeweg et al. retrospectively enrolled consecutive patients admitted to the hospital with a clinical suspicion of acute diverticulitis to develop their clinical scoring system ('CS tool').[7] The patients were admitted between January 2002 and March 2006 and in every patient abdominal computed tomography (CT) was performed to diagnose acute diverticulitis.

Laurell et al. enrolled consecutive patients with acute abdominal pain presenting at a single hospital between February 1997 and June 2000.[14] In this independent cohort ('IND cohort') the clinical presentation of acute diverticulitis was described and the natural history characterized in the short perspective.[14] The aim of this study was not to evaluate the predictive value of variables from the disease history, physical examination and laboratory tests. Therefore, in the current study only those patients were used with complete data sets to allow validation of the two tools.

The two derivation datasets of each tool (ED triad and CS tool) were used to perform a crosswise external validation. Crosswise validation indicates the use of the data of the ED triad cohort to externally validate the CS tool and vice versa. In addition, the two tools were externally validated on a third, independent dataset (IND cohort). All statistical analyses were performed using SPSS® version 18 and SAS® version 9.1.

Study characteristics

Thorough assessment of differences in the included population, definition of outcome and data acquisition in the three cohorts was essential to evaluate the diagnostic performance of the ED triad and the CS tool. Prevalence of diverticulitis, severity of diverticulitis (Hinchey classification), gender, admission rate and the performance of acute/subacute surgery were compared between the different cohorts with chi^2 tests. Median age and hospital stay were compared with Kruskall-Wallis tests. To gain further insight in the differences between the study populations, the frequencies of the variables of both predictive tools were compared.

External validation

ED triad

The ED triad comprehends three variables; tenderness exclusively in the lower left quadrant (LLQ) on physical examination, absence of vomiting and elevated serum C-reactive protein (CRP) >50mg/l. The rule is positive when these variables are present simultaneously and indicative for diverticulitis. The predictive value of the variables expressed in odds ratios (OR's), was calculated in the derivation dataset (ED triad cohort) and recalculated in the validation datasets (CS tool cohort and the IND cohort) with a multivariable regression analysis to provide insight in the relative weight of each variable in the triad. The discriminatory capacity of the ED triad was expressed by calculating the Area Under the Curve (AUC) with the 95% confidence interval (CI). The AUC indicates how well a model distinguishes patients with a high probability of having diverticulitis from patients with a low probability of having diverticulitis. The value of the AUC varies between 0.5 (no extra information above chance), and 1 (indicating perfect discrimination).

The ED triad was developed to have a high positive predictive value to select patients with uncomplicated diverticulitis rendering additional imaging unnecessary. Performance of the triad was therefore evaluated in the validation cohorts by calculating the positive predictive value, the negative predictive value, sensitivity and specificity. If present, patients rendered false positive were described in detail. These patients are of special interest since they might be wrongfully withheld from additional diagnostic tests delaying adequate treatment. Primary analyses were done in patients with complete datasets. Since the ED triad has three variables and the CS tool has seven, the ED triad can be evaluated in more patients of the IND cohort because there are fewer patients with missing data. To evaluate consistency of results separate analysis of the ED triad was performed with these additional patients from the IND cohort.

CS tool

The CS tool includes seven variables; age (two categories), previous episodes of diverticulitis, localization of symptoms, aggravation of pain on movement, localization of tenderness on physical examination, vomiting or not and serum CRP (divided into three categories). Similar to the ED triad the predictive value of each variable in the derivation dataset (CS tool cohort) was compared to the value in the validation datasets (ED triad cohort and IND cohort) to gain insight in the most consistent and strongest contributing variables. Discriminatory capacity was quantified with the AUC and the 95% CI.

Diagnostic accuracy of the CS tool was evaluated by calculating individual probabilities in the derivation cohort. To allow comparison of the diagnostic accuracy of the CS tool with the ED triad, a cut-off was chosen to resemble the aim of the ED triad, namely to have a high positive predictive value (PPV). The value of the cut-off analysis was set at a

calculated probability of 90% to correspond with a PPV of around 90%. The individual probabilities in the validation datasets were calculated using the original values obtained with the regression analysis of the derivation dataset. However, the CS tool was adjusted based on the background prevalence of diverticulitis which is likely to differ between the cohorts. To express discriminatory capacity of the CS tool, AUC's with 95% CI's were calculated with univariable logistic regression analyses of the individual probabilities. Furthermore, the probabilities were used to calibrate the CS tool. Calibration refers to the agreement between predicted presence of acute diverticulitis and the observed rates. The predicted prevalence of diverticulitis per decile of patients was plotted against the observed prevalence in the validation cohorts.

Results

Study characteristics

Patient and study characteristics of the three cohorts are displayed in *Table 1*. There was a substantial difference in selection of patients between the studies. In the ED triad cohort patients were included only whenever additional imaging was deemed necessary based on the clinical judgment of the attending physician, whereas in the IND cohort all patients with acute abdominal pain were included. Patients included in the ED triad derivation cohort and the IND cohort, where patients presented at the ED with acute abdominal pain and data were prospectively assessed. Thereby, also false-negatives had been included in these study cohorts. As a result of the retrospective identification of patients in the CS tool derivation cohort, patients not suspected of having diverticulitis, but with a final diagnosis of diverticulitis were not included (i.e., the false negatives of the clinical diagnosis 'diverticulitis' had not been included in the cohort). Furthermore, in the CS tool cohort, patients were only included whenever hospital admission was deemed necessary.

The final diagnosis in all patients of the ED triad cohort was established in consensus by an expert panel after six months of follow-up, based on all available clinical information. In the CS tool cohort CT was considered the gold standard for diagnosing acute diverticulitis in case of non-operative management. Pathology- and operative reports were used as gold standard in case of operative treatment. In case of another diagnosis than diverticulitis, CT findings and medical records were used to determine the final diagnosis during follow-up. The final diagnosis in the IND cohort had been established by its study coordinator with all clinical information available in a follow-up period of at least one year (up to three years). One-hundred and three patients of the 145 patients suspected of having diverticulitis in the IND cohort were included in the current study due to missing data in the remaining 42 patients. An additional separate analysis of the ED triad was performed in 126 patients of the IND cohort to examine consistency of results. Twenty-three additional patients could be included since they had complete data for the evaluation of the ED triad but missing data to evaluate the CS tool. The prevalence of the

final diagnosis of diverticulitis was significantly different between the ED triad cohort (63%), the CS tool cohort 43% and the IND cohort (56%) (p=0.01). Diverticulitis was more severe in the CS tool cohort where 33% of patients had complicated diverticulitis (Hinchey classification ≥2) compared to 8% of patients in the ED triad cohort and 5% in the IND cohort (p<0.01). Median age did not differ between patients with a final diagnosis of diverticulitis and those that had another final diagnosis in the ED triad and CS tool cohort. However, patients were slightly older in the IND cohort compared to the two derivation cohorts (p<0.01).

Table 1: Comparison of study and patient characteristics between the emergency department triad derivation cohort, the clinical scoring tool derivation cohort and the independent cohort

	ED[a] triad cohort		CS[b] tool cohort		IND[c] cohort	
Study characteristics						
Patient selection	Prospective inclusion of patients with acute abdominal pain for >2 hours and less than 5 days, warranting additional radiological examination		Retrospective inclusion of patients admitted to the hospital with acute abdominal pain and clinical suspicion of acute diverticulitis based on the CT application form		Prospective inclusion of patients with acute abdominal pain for <7 days	
Reference standard	Expert panel consensus based on all available clinical information obtained in a follow-up of 3 months		In case of non-operative treatment CT was reference standard, whenever the final diagnosis was not diverticulitis, CT findings were complemented with the medical chart to execute as reference standard		All available clinical information obtained in a follow-up period of at least 1 year up to 3 years was used to establish the final diagnosis by the first author	
Patient characteristics						
	No diverticulitis	**Diverticulitis**	**No diverticulitis**	**Diverticulitis**	**No diverticulitis**	**Diverticulitis**
N patients	46	80	163	124	45	58
Age[d]	54 (43-66)	58 (50-70)	53 (40-67)	59 (51-68)	67 (54-76)	62 (52-75)
Gender (% female)	67%	56%	63%	60%	78%	67%
Admission rate	59%	55%	100%	100%	87%	95%
Hospital stay[d]	4 (3-8)	5 (4-7)	not recorded	6 (4-12)	3 (2-5)	3 (2-4)
Hinchey class ≥2 (%)	na[e]	6 (8%)	na[e]	41 (33%)	na[e]	3 (5%)
Acute/subacute colonic surgery for diverticulitis	na[e]	13 (16%)	na[e]	31 (25%)	na[e]	1 (2%)

[a] Emergency department
[b] Clinical scoring
[c] Independent
[d] Median an interquartile range
[e] Not applicable

Table 2 displays the frequencies of all the variables included in both tools. All three variables in the ED triad are part of the CS tool be it with minor adjustments. A history of one or more previous episodes of diverticulitis is part of the CS tool. However, it was not recorded in the ED triad derivation cohort prohibiting the display of the frequencies. Moreover, the lack of this information compels to perform the external validation without this variable. Apart from some variance, patterns of frequencies were consistent between the ED triad, CS tool and IND cohort for age, tenderness in the lower left quadrant on physical examination, anamnestic localization of pain, CRP and absence of vomiting. Pain on movement was the only variable that showed an opposite distribution between the ED triad cohort and the CS tool and IND cohorts in patients with and without diverticulitis.

Table 2: Frequencies of variables included in both predictive tools

	ED[a] triad cohort		CS[b] tool cohort		IND[c] cohort	
Variables in ED[a] triad and CS[b] tool						
	No diverticulitis	**Diverticulitis**	**No diverticulitis**	**Diverticulitis**	**No diverticulitis**	**Diverticulitis**
N patients	46	80	163	124	45	58
Age >50 years	59% (27)	74% (59)	57% (93)	78% (97)	78% (35)	85% (49)
Previous episode(s)	not reported	not reported	7% (11)	35% (44)	44% (18)[d]	61% (35)[d]
Tenderness LLQ[e]	13% (6)	49% (39)	33% (53)	73% (90)	22% (10)	52% (30)
CRP[f]						
- ≤10 (reference)	28% (13)	1% (1)	28% (46)	11% (14)	51% (23)	14% (8)
- 11-49	39% (18)	18% (14)	27% (44)	21% (26)	16% (7)	19% (11)
- ≥50	33% (15)	81% (65)	45% (73)	68% (84)	33% (15)	67% (39)
Pain localization history						
- RLQ[g] (reference)	11% (5)	5% (4)	27% (44)	5% (6)	20% (9)	28% (16)
- LLQ[e]	20% (9)	50% (40)	27% (44)	65% (81)	29% (13)	57% (33)
- Diffuse/Other	70% (32)	45% (36)	46% (75)	30% (37)	51% (23)	16% (9)
Pain on movement	46% (21)	43% (34)	33% (53)	59% (73)	44% (20)	53% (31)
Absence of vomiting	61% (28)	95% (76)	66% (108)	80% (99)	73% (33)	91% (53)

[a] Emergency department
[b] Clinical scoring
[c] Independent
[d] Unknown for four patients in the no diverticulitis group and one in the diverticulitis group, percentages were calculated without these patients
[e] Left lower quadrant
[f] C-reactive protein
[g] Right lower quadrant

External validation

ED triad

Table 3 displays the relative weight and predictive value of the three variables of the ED triad in the derivation cohort as well as in its validation cohorts (CS tool cohort and IND cohort). In the derivation cohort the absence of vomiting was the most important predictive variable with an odds ratio (OR) of 16.32 (95% CI: 3.70-72.07) while it was the least important variable in the CS tool cohort where the OR was 2.12 (95% CI: 1.14-3.93). For all three variables the predictive value in the validation cohorts was less than in the derivation cohort. This is illustrated by the difference in discriminatory capacity expressed in the AUC that was good in the ED triad derivation cohort (0.86, 95% CI: 0.80-0.93) versus fair in the CS tool cohort (0.77, 95%CI: 0.72-0.83) and the IND cohort (0.73, 95%CI: 0.63-0.82).

Out of the 30 patients in the derivation cohort (24% of the cohort) of which the ED triad was positive, 29 had a final diagnosis of diverticulitis. This makes the performance of the ED triad highly adequate with a PPV of 97% (*Table 4*). However, two of the patients who would not have received imaging based on a positive outcome of the rule, had complicated diverticulitis warranting operative intervention. In the CS tool cohort all three variables were present simultaneously in 57 patients making up 20% of the total cohort (*Table 4*). Of these, 11 patients did not have a final diagnosis of diverticulitis, resulting in a PPV of 81%. In at least five of them, delay of treatment as a result of refrained imaging could have had serious consequences (acute appendicitis, adnexitis, anastomotic leakage, two tumors of the sigmoid). Of the remaining 46 patients who did have diverticulitis 7 had complicated diverticulitis warranting an intervention. The ED triad was positive in 14 out of 103 patients in the IND cohort (14% of the cohort). The PPV of the ED triad was 100% so no patients with a positive triad had an alternative final diagnosis other than diverticulitis (*Table 4*). The separate analysis including the additional patients with complete data (*N*=126) from the IND cohort show similar results. The AUC of the ED triad is the same as in the primary analysis with slightly different confidence intervals (0.73, 95% CI: 0.64-0.81). The ED triad was positive in 17 out of 126 patients identifying 13% of the cohort. The NPV (51%, 95% CI: 42%-61%), sensitivity (22%, 95% CI: 14%-33%) and specificity (97%, 95% CI: 88%-99%) were comparable as well. The PPV was lower (88%, 95% CI: 66%-97%) than in analysis of the IND cohort with 103 patients. In the separate analysis two patients were classified false positive having nonspecific abdominal pain as final diagnosis.

CS tool

The predictive value of the six available variables of the CS tool was recalculated in the derivation cohort with a multivariable regression analysis since the variable 'previous episodes' was not recorded in the ED triad cohort. *Table 3* displays the regression coefficients and OR's of the CS tool in the derivation cohort as well as in its validation cohorts (ED triad cohort and IND cohort). In the derivation cohort and in the IND cohort

pain on movement is predictive for diverticulitis (OR; 4.00, 95% CI; 2.15-7.42 and 1.98, 95% CI; 0.70-5.60), whereas in the ED triad cohort it is predictive for not having diverticulitis (OR; 0.60, 95% CI; 0.21-1.77). The predictive value of age, CRP and absence of vomiting was higher in the validation cohorts. Only the reported localization of the pain had less predictive value than in the derivation cohort. Furthermore, localization of pain in the LLQ on examination had a higher predictive value in the ED triad cohort but less predictive value in the IND cohort. The multivariable discriminatory capacity without fixed regression coefficients was good in the CS tool derivation cohort (AUC; 0.84, 95% CI; 0.80-0.89), and even somewhat higher in the ED triad and IND cohorts (AUC; 0.89, 95% CI; 0.82-0.95 and 0.85, 95% CI; 0.78-0.92).

Table 3: Odds ratios with 95% confidence intervals of the variables of the emergency department triad and the clinical scoring tool in the derivation cohorts and the independent cohort

	ED[a] triad cohort		CS[b] tool cohort		IND[c] cohort	
	OR[d]	**95% CI[e]**	**OR[d]**	**95% CI[e]**	**OR[d]**	**95% CI[e]**
ED[a] triad						
Intercept	0.03	na[f]	0.08	na[f]	0.18	na[f]
CRP[g] >50	8.98	3.43-24.13	3.84	2.18-6.79	2.98	1.22-7.30
Tenderness LLQ[h]	6.21	1.96-19.73	6.41	3.66-11.22	3.86	1.54-9.69
Absence of vomiting	16.32	3.70-72.07	2.12	1.14-3.93	3.58	1.03-12.49
AUC[i] (95% CI[e])	**0.86 (0.80-0.93)**		**0.77 (0.72-0.83)**		**0.73 (0.63-0.82)**	
CS[b] tool						
Intercept	0.00	na[f]	.006	na[f]	.049	na[f]
Age >50 years	2.43	0.79-7.52	2.28	1.17-4.45	2.58	0.70-9.50
Tenderness LLQ[h]	3.44	0.60-19.63	3.42	1.69-6.92	2.02	0.53-7.70
CRP[g]						
- ≤10 (reference)	1.0	na[f]	1.0	na[f]	1.0	na[f]
- 11-49	19.14	1.57-232.78	1.80	0.72-4.52	2.62	0.60-11.34
- ≥50	116.06	9.52-1415.49	4.71	2.04-10.84	7.50	2.34-24.07
Pain localization history						
- RLQ[j] (reference)	1.0	na[f]	1.0	na[f]	1.0	na[f]
- LLQ[h]	2.34	0.22-24.98	7.94	2.50-25.18	0.87	0.20-3.87
- Diffuse	1.03	0.15-7.09	3.50	1.20-10.25	0.15	0.04-0.61
Pain on movement	0.60	0.21-1.77	3.99	2.15-7.42	1.98	0.70-5.60
Absence of vomiting	20.26	4.20-97.77	2.10	1.06-4.13	4.79	1.16-19.88
AUC[i] (95% CI[e])	**0.89 (0.82-0.95)**		**0.84 (0.80-0.89)**		**0.85 (0.78-0.92)**	

[a] Emergency department
[b] Clinical scoring
[c] Independent
[d] Odds ratio
[e] Confidence interval
[f] Not applicable
[g] C-reactive protein
[h] Left lower quadrant
[i] Area Under the Curve in the Receiver Operating Characteristics curve
[j] Right lower quadrant

Only 18 (6%) patients in the CS tool cohort had a probability above 90%. Two of these did not have diverticulitis. As a consequence the 90% probability cut-off value corresponded with a PPV of 89% (*Table 4*). With fixed values for the variables of the CS tool and adjustment to differences in prevalence of diverticulitis the AUC was good in the ED triad cohort (0.81, 95% CI; 0.73-0.89) and fair in the IND cohort (0.71, 95% CI; 0.61-0.81). Without adjustment of the CS tool to differences in prevalence it systematically underestimated the probability of diverticulitis. *Figure 1* depicts this calibration and shows improved calibration after adjustment of the model especially in the ED triad cohort. After adjustment of the intercept the CS tool assigned a probability of >90% to 24 (19%) of the patients in the ED triad cohort and 9 (9%) in the IND cohort. The PPV was 92% in the ED triad cohort and 89% in the IND cohort (*Table 4*).

Table 4: Performance parameters with 95% confidence intervals of the emergency department triad and the clinical scoring tool at a cut-off predicted probability of 90% in the three cohorts

	ED[a] triad cohort	**CS[b] tool cohort**	**IND[c] cohort**
	% (95% CI[d])	**% (95% CI[d])**	**% (95% CI[d])**
ED[a] triad			
PPV[e]	97 (83-99)	81 (69-89)	100 (78-100)
NPV[f]	47 (37-57)	66 (60-72)	51 (40-61)
Sensitivity	36 (27-47)	37 (29-46)	24 (1-37)
Specificity	98 (89-100)	93 (88-96)	100 (92-100)
Patients identified	24	20	14
CS[b] tool			
PPV[e]	92 (74-98)	89 (67-97)	89 (57-98)
NPV[f]	76 (67-84)	67 (60-72)	47 (37-57)
Sensitivity	48 (34-62)	17 (11-26)	14 (7-25)
Specificity	98 (91-99)	99 (95-100)	98 (88-100)
Patients identified	19	6	9

[a] Emergency department
[b] Clinical scoring
[c] Independent
[d] Confidence interval
[e] Positive predictive value
[f] Negative predictive value

Discussion

The performance of a predictive tool is prone to be overestimated in the derivation cohort. That is why external validation is of crucial importance prior to widespread use in daily clinical practice. Validation of tools in as many different settings as possible creates insight in the applicability and reliability. Therefore, we included not only the crosswise external validation, but also an independent cohort (IND cohort) for external validation.

This cohort especially provides more information about where the differences found in predictive capacity originate. For instance, the diagnostic performance of both tools was better in the ED triad and IND cohort then in the CS tool cohort. This finding suggests that there is a systematic difference between the three cohorts influencing the predictive capacity. We propose that the described study characteristics and more specifically patient selection plays a major role. In the CS tool cohort patients are all hospitalized, whereas in the ED triad and the IND cohort this is not a selection criterion. Logically, patients needing admittance to the hospital are in worse condition than those who are treated on an outpatient basis. This is illustrated in the comparison of the Hinchey classification of the cohorts; a third (33%) of the patients in the CS tool cohort has complicated diverticulitis compared to only 8% in the ED triad cohort and 5% in the IND cohort. Patients with a higher Hinchey classification are more frequently in need of acute interventions. The disadvantage of predictive tools is that they do not only have to distinguish between the presence of illness and no illness, but also have to distinguish between diverticulitis and other abdominal conditions, for instance appendicitis. Not only were the patients in the CS tool cohort with a final diagnosis of diverticulitis more severely ill, but it is plausible that the patients with a different final diagnosis in this cohort were also more severely ill and that they had more acute underlying abdominal conditions needing intervention. The increasing difficulty to distinguish between the more severely ill patients is illustrated in *Table 1* where the differences between patients with and without diverticulitis are smaller in the CS tool cohort then in its validation cohorts (ED triad cohort and IND cohort). There is substantial variance in the OR's of the variables included in both tools across the different cohorts. Most striking is the high predictive value of CRP levels >50mg/l and absence of vomiting in the ED triad cohort compared to the other two cohorts who have more similar OR's. Disease severity of the cohorts might play a role, however it cannot fully account for the differences found since the ED triad cohort and the IND cohort are more alike in terms of disease severity compared to the CS tool cohort. Differences in the way clinicians identify patients to be suspected of having acute diverticulitis could have led to selection bias. For example, the way primary care is organized differs between countries (ED triad cohort and CS tool cohort versus IND cohort), which might have influenced patient selection. Unfortunately a large part of this selection process is not well described, so most factors remain elusive. The separate analysis of the ED triad with additional patients in the IND cohort illustrates that the performance of the model is consistent with the same AUC and comparable NPV, sensitivity and specificity. Only the PPV was lower in than in the primary analysis (88% versus 100%) because of two false positive classifications. However, as these two patients had nonspecific abdominal pain as their final diagnosis they did not warrant direct imaging. The aim of both predictive tools was to aid the clinical diagnosis and primarily prevent unnecessary additional imaging. However, to be useful in clinical practice the tool must be applicable to a substantial proportion of patients suspected of diverticulitis. The ED triad identified a more substantial part of patients (24% in the ED triad cohort, 20% in the CS tool cohort and 14% in the IND cohort) with high positive predictive values in the

ED triad cohort (97%) and the IND cohort (100%). However, in the CS tool cohort the PPV was only 81% which is substantially lower than the PPV of the CS tool in all three cohorts (CS tool cohort 89%, ED triad cohort 92%, IND cohort 89%). The CS tool fell short in identifying a substantial proportion of patients with diverticulitis; only 6% in the derivation cohort, 19% in the ED triad cohort and 9% in the IND cohort. Two surveys revealed that surgeons would use imaging in 8 out of 10 (87% and 72%, respectively) patients suspected of diverticulitis.[3, 4] On average the ED triad identifies 19% of patients which would result in a 15% decrease of imaging, while the CS tool identifies 11% and thus would reduce imaging by 9%. A shortcoming of this study is that the occurrence of previous episodes of diverticulitis was not recorded in the ED triad cohort prohibiting the external validation of the original CS tool that included this variable, especially since this was the variable with the best predictive value in the CS tool. (OR 5.67, 95% CI 2.36-13.62). In the IND cohort more patients with a final diagnosis of diverticulitis had a previous episode (61%) compared to patients with another diagnosis (44%), indicating that it could have predictive value. There is, however, some limitation to the use of this variable in a clinical decision rule. In the CS tool cohort 35% of patients with a final diagnosis of diverticulitis had one or more previous episodes of diverticulitis. As a consequence, the rule would only identify a third of the patients on forehand and will turn out even lower when we account for the fact that there are more variables in the rule.

Identification of variables with predictive value for the diagnosis of diverticulitis is feasible. Despite the fact that the two recent predictive tools have been developed independently, both analyses ended up with the same variables that have the best predictive value in diagnosing acute colonic diverticulitis. All three variables that constitute the ED triad are included in the CS tool, be it with minor adaptations.

Isolated tenderness in the LLQ on examination, CRP >50mg/l and absence of vomiting have significant predictive value in patients with suspected acute diverticulitis. With additional variables present (older age, pain on movement, previous episode) the certainty of the diagnosis could be increased. By using these variables the need of additional imaging to diagnose acute diverticulitis may be reduced.

Reference list

1 Lameris W, van Randen A, van Gulik TM et al. A clinical decision rule to establish the diagnosis of acute diverticulitis at the emergency department. Dis Colon Rectum 2010;53:896-904.

2 Rafferty J, Shellito P, Hyman NH et al. Practice parameters for sigmoid diverticulitis. Dis Colon Rectum 2006;49:939-944.

3 Munikrishnan V, Helmy A, Elkhider H et al. Management of acute diverticulitis in the East Anglian region: results of a United Kingdom regional survey. Dis Colon Rectum 2006;49:1332-1340.

4 Schechter S, Mulvey J, Eisenstat TE. Management of uncomplicated acute diverticulitis: results of a survey. Dis Colon Rectum 1999;42:470-475.

5 Cho KC, Morehouse HT, Alterman DD et al. Sigmoid diverticulitis: diagnostic role of CT--comparison with barium enema studies. Radiology 1990;176:111-115.

6 Wexner SD, Dailey TH. The initial management of left lower quadrant peritonitis. Dis Colon Rectum 1986;29:635-638.

7 Andeweg CS, Knobben L, Hendriks JC et al. How to Diagnose Acute Left-sided Colonic Diverticulitis: Proposal for a Clinical Scoring System. Ann Surg 2011;253:940-946.

8 Altman DG, Royston P. What do we mean by validating a prognostic model? Stat Med 2000;19:453-473.

9 Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-387.

10 Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. Ann Intern Med 1999;130:515-524.

11 Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. Ann Intern Med 2006;144:201-209.

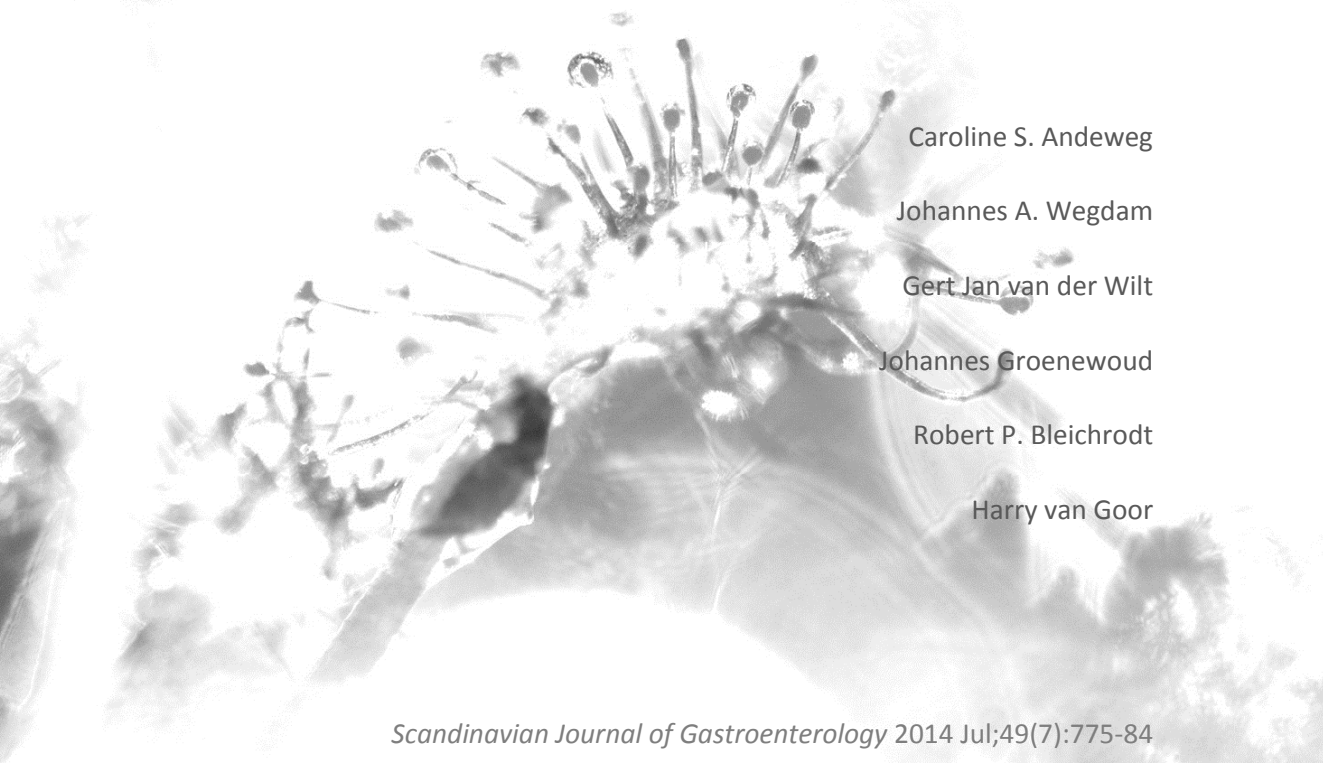
12 Steyerberg EW. Clinical Prediction Models. Springer-Verlag New York, 2008.

13 Lameris W, van Randen A, van Es HW et al. Imaging strategies for detection of urgent conditions in patients with acute abdominal pain: diagnostic accuracy study. BMJ 2009;338:b2431-

14 Laurell H, Hansson LE, Gunnarsson U. Acute diverticulitis--clinical presentation and differential diagnostics. Colorectal Dis 2007;9:496-501.

Chapter 4

Toward an evidence based step-up approach in diagnosing diverticulitis



Caroline S. Andeweg

Johannes A. Wegdam

Gert Jan van der Wilt

Johannes Groenewoud

Robert P. Bleichrodt

Harry van Goor

Scandinavian Journal of Gastroenterology 2014 Jul;49(7):775-84

Abstract

Background
The lack of pathognomonic findings and the chance of complicated disease have resulted in the widespread use of additional imaging to diagnose acute colonic diverticulitis (ACD). The added value of additional imaging in the diagnostic work-up of patients suspected of ACD is not well defined.

Aims
The aim of this study was to systematically review the literature of the accuracy of the clinical evaluation and diagnostic modalities for patients with suspected ACD, to come to an evidence-based approach to diagnose ACD.

Methods
A systematic review and meta-analysis of studies that reported diagnostic accuracy of the clinical diagnosis and diagnostic modalities in patients with suspected diverticulitis were performed. Study quality was assessed with the STARD checklist. TP, TN, FP and FN findings were extracted and pooled estimates of sensitivity and specificity per diagnostic test were calculated, if applicable.

Results
The overall quality of the studies reporting the diagnostic accuracy of the clinical diagnosis, contrast enema and MRI were moderate to poor and not suitable for meta-analysis. Sensitivity of the clinical diagnosis varied between 64% and 68%. US and CT studies were eligible for meta-analysis. Summary sensitivity estimates for US were 90% (95% CI: 76%-98%) versus 95% (95% CI: 91%-97%) for CT (p=0.86). Summary specificity estimates for US were 90% (95% CI: 86%-94%) versus 96% (95% CI: 90%-100%) for CT (p=0.04). Sensitivity for MRI was 98% and specificity varied between 70% and 78%. Sensitivity of contrast enema studies varied between 80% and 83%.

Conclusions
In two-thirds of the patients the diagnosis of ACD can be made based on clinical evaluation alone. In one-third of the patients, additional imaging is a necessity to establish the diagnosis. US and CT are comparable in diagnosing diverticulitis and superior to other modalities. CT has the advantage of higher specificity and the ability to identify alternative diagnoses. The role of MRI is not yet clear in diagnosing ACD. Contrast enema is considered an obsolete imaging technique to diagnose ACD based on lower sensitivity and specificity than US and CT. A step-up approach with CT performed after an inconclusive or negative US, seems a logical and safe approach for patients suspected of ACD.

Introduction

Diverticulosis is a common disorder affecting approximately 65% of the population over 65 years. Twenty-five percent of these patients will suffer one or more episodes.[1] Patients with acute colonic diverticulitis (ACD) impose a large burden to national healthcare. Recent evidence suggests that rates of treatment for ACD have increased over the last decade.[2]

The lack of pathognomonic findings and the chance of complicated disease have resulted in the widespread use of additional imaging to diagnose ACD. With only about 10% of patients presenting with complicated disease, additional imaging is not beneficiary in the majority of patients.[3, 4] Although important, the added value of additional imaging to clinical in the diagnostic work-up of patients suspected of ACD is not well defined. This prompted us to systematically review the literature to establish an evidence-based approach to diagnose ACD, taking into consideration patient's burden and safety and efficient use of diagnostic resources.

Methods

Search strategy

The following databases were searched to identify studies reporting on diagnostic accuracy of the clinical diagnosis and imaging modalities in patients with suspected ACD: Pubmed, Medline and Embase and the Cochrane Library of Systematic Reviews. The search strategies were adapted to the different databases to maximize yield. All keywords suited for the different databases were used in different order to expose the maximum amount of hits relevant to the subject. All terms used are shown in *Table S1*. Only publications in the English, German and Dutch language were used and publications before 1980 were excluded. Only full text studies were included for the purpose of retrieving data since abstracts alone do not contain all information necessary to score the quality of a study. All selected studies were reviewed for cross-references. After completion of the review, the search was repeated to detect the latest reported studies, the most recent being December 2013.

Selection criteria

All studies designed to evaluate the diagnostic performance of any diagnostic test in patients with suspected ACD were considered. Two reviewers independently reviewed all abstracts (CA and JW) and selected relevant studies according to the following criteria: Prospective studies that reported the number of true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) or provided enough information to extract them from the study report. Only those studies were selected for review that defined a reliable reference for the presence or absence of ACD and that adequately defined and

reported patient recruitment criteria. Articles that met the above criteria were again subjected to inclusion criteria, but this time to judge the eligibility for meta-analysis. Only studies that evaluated a consecutive series of patients with suspected ACD were included for meta-analysis.

Assessment of methodological quality

All selected papers were evaluated for methodological quality according to the Standards for Reporting of Diagnostic Accuracy (STARD) initiative.[5] The STARD initiative is a 25-item checklist to improve the quality of the reporting of diagnostic accuracy studies. The results of the quality appraisal can be summarized to offer a general impression of the validity of the available evidence. Three authors (CSA, JAW and RPB) independently completed the STARD checklist of each paper and in case of different outcomes the definitive answer was reached by consensus. The STARD checklist was completed based on the information clearly enunciated in the published article without attempting to make contact with its authors to seek clarification. (*Table S2*)

Data extraction and meta-analysis

Data were extracted only from full articles and summarized using the data extraction sheet as provided by the STARD initiative group. Meta-analysis, if applicable, was conducted and heterogeneity between selected studies was assessed on patient characteristics (age and percentage women), presence of diverticulitis (presences of both diverticula and bowel wall thickening on US or CT) or complicated diverticulitis (ACD with pericolic abscesses or signs of perforation or fistula) and reference testing (percentage of patients with a high validity reference test, i.e., histopathological confirmation after surgery or colonoscopy with biopsy).

For each variable, a weighted average with corresponding 95% confidence interval (CI) was calculated. Homogeneity between the studies was defined if the standard deviation of a variable was less than 20% of the weighted average. Standard test characteristics (TP, TN, FP, FN findings) were extracted and positive and negative likelihood ratios (LR+ and LR-, respectively) were calculated. Pooled estimates of sensitivity and specificity per diagnostic test, including 95% CI's were calculated using StatsDirect, using the random effects model. Differences in sensitivity and specificity per diagnostic modality were tested for statistical significance using logistic regression analysis, with sensitivity or specificity as dependent variable and diagnostic test as independent variable. Heterogeneity within subgroups was estimated by calculating Cochran's Q statistic. Logistic regression analysis was conducted in SAS 8.2, using proc-logistic. A p-value <0.05 was considered statistically significant.

Results

Search results

Fifteen studies evaluating diagnostic accuracy of the clinical evaluation and imaging modalities in patients with suspected ACD were retrieved from the databases, of which eight were eligible for meta-analysis. Search results are displayed in *Figure 1*. Most studies were of moderate quality according to the STARD checklist and are discussed separately. A summary of the diagnostic accuracy of the clinical evaluation and diagnostic modalities in patients suspected of ACD is given in *Table 1*.

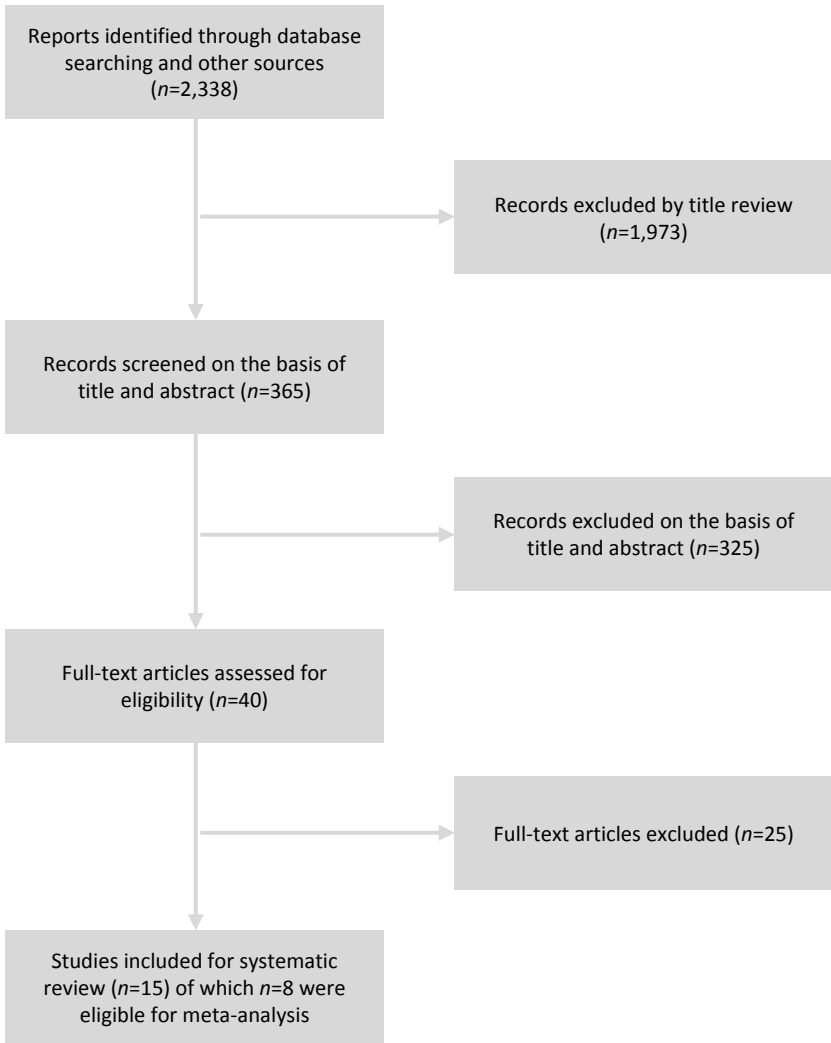


Figure 1: Flow chart of search results and study selection

Table 1: Summary of the diagnostic accuracy of the clinical evaluation and diagnostic modalities in patients suspected of acute colonic diverticulitis (ACD)

Study/year	Participants with ACD		Participants without ACD		Sensitivity	Specificity	PPV	NPV	LR+ (95% CI)	LR- (95% CI)
	TP	FN	TN	FP						
Clinical evaluation										
Laurell, 2006	93	52	1,049	46	0.64	0.97	0.67	0.95	15.27 (11.22–20.77)	0.37 (0.30–0.47)
Toorenvliet, 2008	30	14	728	16	0.68	0.98	0.65	0.98	32 (18.75–53.60)	0.33 (0.21–0.50)
US										
Verbanck, 1989	44	8	57	14	0.85	0.80	0.75	0.88	4.29 (2.65–6.96)	0.19 (0.10–0.37)
Schwerk, 1992	51	1	76	2	0.98	0.97	0.96	0.99	38.25 (9.73–150.31)	0.02 (0.003–0.14)
Farag Soliman, 2004	43	0	20	0	1.00	1.00	1.00	1.00	Infinity†	0
US (studies included in meta-analysis)										
Zielke, 1997	62	12	64	5	0.84	0.93	0.93	0.84	11.56 (4.94–27.05)	0.17 (0.10–0.29)
Pradel, 1997	28	5	26	5	0.85	0.84	0.85	0.87	5.26 (2.33–11.89)	0.18 (0.08–0.41)
Hollerweger, 2001	96	6	71	2	0.94	0.97	0.98	0.92	34.35 (8.74– 34.87)	0.06 (0.03–0.14)
Summary estimate (95% CI) ¶					0.90 (0.76–0.98)	0.90 (0.86–0.94)	0.93 (0.84–0.98)	0.88 (0.82–0.92)	12.83 (7.42–22.19)	0.12 (0.08–0.17)

Table 1 (continued): Summary of the diagnostic accuracy of the clinical evaluation and diagnostic modalities in patients suspected of acute colonic diverticulitis (ACD)

Study/year	Participants with ACD		Participants without ACD		Sensitivity	Specificity	PPV	NPV	LR+ (95% CI)	LR- (95% CI)
	TP	FN	TN	FP						
CT										
Doringer, 1990	20	1	9	3	0.95	0.75	0.87	0.90	3.81 (1.42-10.20)	0.06 (0.01-0.44)
Farag Soliman, 2004	42	1	20	0	0.98	1.00	1.00	0.95	Infinity†	0.02†
CT (studies included in meta-analysis)										
Cho, 1990	25	2	29	0	0.93	1.00	1.00	0.94	Infinity†	0.07
Stefánsson, 1997	36	16	36	0	0.69	1.00	1.00	0.69	Infinity†	0.31
Pradel, 1997	30	3	24	7	0.91	0.77	0.81	0.89	4.03 (2.08-7.79)	0.12 (0.04-0.35)
Rao, 1998	62	2	86	0	0.97	1.00	1.00	0.98	Infinity†	0.03
Werner, 2003	65	2	52	1	0.97	0.98	0.98	0.97	51.42 (7.38-358.46)	0.03 (0.01-0.12)
Tack, 2005	36	3	70	1	0.92	0.99	0.98	0.96	65.654 (9.34-459.83)	0.08 (0.03-0.23)
Summary estimate (95% CI) ¶					0.95 (0.91-0.97)	0.96 (0.90-1.00)	0.97 (0.92-0.99)	0.91 (0.82-0.97)	30.62 (16.07-58.36)	0.10 (0.07-0.15)

Table 1 (continued): Summary of the diagnostic accuracy of the clinical evaluation and diagnostic modalities in patients suspected of acute colonic diverticulitis (ACD)

Study/year	Participants with ACD		Participants without ACD		Sensitivity	Specificity	PPV	NPV	LR+ (95% CI)	LR- (95% CI)
	TP	FN	TN	FP						
MRI										
Heverhagen, 2008 Observer 1	45	1	7	2	0.98	0.78	0.96	0.88	4.40 (1.30-14.96)	0.03 (0.004-0.20)
Heverhagen, 2008 Observer 2	46	1	7	3	0.98	0.70	0.94	0.88	3.26 (1.26-8.42)	0.03 (0.004-0.22)
Contrast Enema										
Cho,1990	20	5	25	0	0.80	1.00	1.00	0.83	Infinity[†]	0.20
Stefánsson, 1997	43	9	29	7	0.83	0.81	0.86	0.76	4.25 (2.16-8.36)	0.21 (0.12-0.40)

ACD: acute colonic diverticulitis
Sensitivity calculated as TP/(TP+FN)
Specificity calculated as TN/(TN+FP)
PPV: positive predictive value, calculated as TP/(TP+FP)
NPV: negative predictive value, calculated as TN/(TN+FN)
LR+: likelihood ratio for positive test, calculated as (sensitivity/1-specificity)
LR-: likelihood ratio for negative test, calculated as (1-sensitivity/specificity)
CI: confidence interval
Π summary estimates of articles included in meta-analysis with 95% CI as calculated with the random effect model
† confidence Intervals not estimable

Clinical evaluation

Two studies reporting on diagnostic accuracy of clinical evaluation in patients suspected of ACD were eligible for inclusion. Both studies were of moderate quality and did not report a consecutive series of patients, hence were not included for meta-analysis.[6, 7] Sensitivities and specificities of the clinical evaluation in patients suspected of ACD varied between 64%-68% and 97%-98%, respectively. Laurell[7] discussed the role of clinical findings and basic laboratory tests separately. They reported that isolated left abdominal tenderness, signs of constipation and a higher level of C-reactive protein (CRP) (73 (95% CI: 63-84) vs 20 (95% CI: 17-22) were more frequent findings in patients with ACD. Vomiting and right-sided abdominal pain were more frequent in patients with non-specific abdominal pain.

Imaging modalities

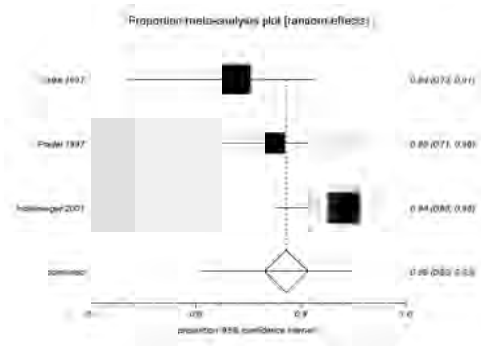
Ultrasound (US)

Six studies reported on diagnostic accuracy of graded compression US. Three studies were of moderate quality and did not report a consecutive series of patients.[8-10] The remaining three studies were of moderate[11, 12] to good quality [13] and were included for meta-analysis. These studies encompassed a total of 382 patients with clinical suspicion of ACD, who underwent graded compression US. Sensitivities and specificities with corresponding confidence intervals of graded compression US and with the results of the Q- and I^2-test are presented in *Figure 2*. Summary estimates for US were 90% (95% CI: 76%-98%) for sensitivity and 90% (95% CI: 86%-94%) for specificity.

Computed Tomography (CT)

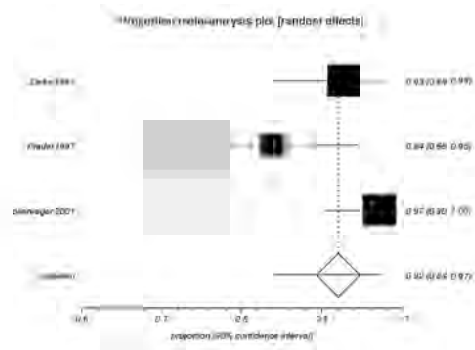
Eight studies reported on diagnostic accuracy of CT in diagnosing ACD, were included. Two were of moderate quality and did not report a consecutive series of patients.[10, 14] The remaining six studies were of moderate[15-19] to good quality[13] and were included for meta-analysis. These studies encompassed a total of 588 patients with clinical suspicion of ACD, who underwent CT. Sensitivities and specificities with corresponding confidence intervals of CT and with the results of the Q- and I^2-test are presented in *Figure 2*. Summary estimates for CT were 95% (95% CI: 91%-97%) for sensitivity and 96% (95% CI: 90%-100%) for specificity.

US Sensitivity



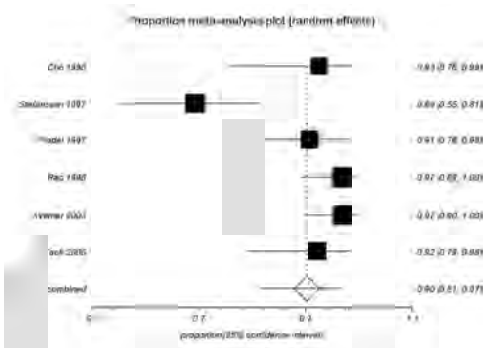
Total events: 382
Test for heterogeneity: Cochran Q = 5,15 (df = 2)
p = 0.08; I^2 = 61.6%

US Specificity



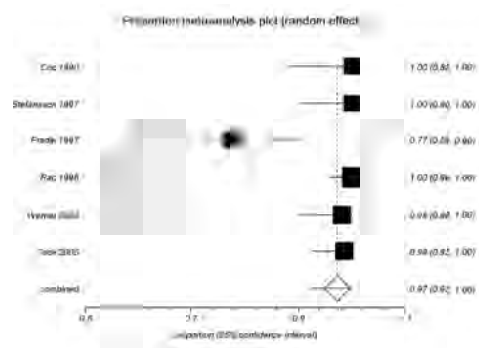
Total events: 382
Test for heterogeneity: Cochran Q = 5,40 (df = 2)
p = 0.07; I^2 = 63%

CT Sensitivity



Total events: 588
Test for heterogeneity: Cochran Q = 24,04 (df = 5)
p = 0.0002; I^2 = 79.2%

CT Specificity



Total events: 382
Test for heterogeneity: Cochran Q = 5,40 (df = 2)
p = 0.07; I^2 = 63%

Figure 2: Proportion meta-analysis plots depicting sensitivity and specificity using the random effects model in prospective studies evaluating graded compression ultrasound and CT in consecutive patients with the clinical diagnosis of acute colonic diverticulitis

Comparison of US and CT

Pooled sensitivity of US 90% (95% CI: 76%-98%) and CT 95% (95% CI: 91%-97%) were comparable (*p*=0.86; OR 1.12; 95% CI: 0.32-3.94). The pooled specificity of CT 96% (95% CI: 90%-100%) was significantly higher compared to US 90% (95% CI: 86%-94%) (*p*=0.04; OR 2.46; 95% CI: 1.01-5.96). Age, gender and type of reference test did not explain the differences in sensitivity and specificity between the two imaging modalities.

The evaluated studies showed homogeneity regarding age, gender and incidence of complicated ACD. Heterogeneity existed in the incidence of ACD and the percentage of patients that underwent high validity reference testing. (*Table 2*) Definitions criteria of ACD and complicated ACD varied between studies. (*Table S2*)

Fifty-five percent of the patients in the US group had ACD as a final diagnosis as compared to 49% in the CT group (*p*=0.04). To determine whether US or CT is better to detect alternative diagnoses, the percentages of patients in whom the diagnosis was truly based on the initial US or CT findings were compared. An accurate diagnosis was made in 68% of patients with a CT scan and in 48% with US (*p*=0.002; OR 2.6; CI: 1.41-4.93). (*Table 3*) False-positive (US 3%; CT 2%) and false-negative (US 6%; CT 5%) results were similar for US and CT.

Magnetic resonance imaging (MRI)

For MRI only one moderate quality study was included.[20] Two investigators, blinded to all clinical, laboratory and radiologic results independently evaluated MRI images of 55 patients suspected of having ACD. Reference standard for the diagnosis of diverticulitis was a combination of surgery and histopathology findings (29%) and clinical follow-up including US of at least three months (71%). Thirty-one patients (57%) additionally underwent abdominal CT in follow-up. Sensitivities of MRI to diagnose ACD in this study were 94% and 96% for both investigators. Specificity was 88%, and the same for both investigators.

Table 2: Independent variables extracted from prospective studies not included in meta-analysis dealing with diagnostic accuracy to diagnose acute colonic diverticulitis (ACD)

Study/year	Diagnostic modality	*n*	Mean age (range)	Women, *n* (%)	Participants with ACD (%)	Participants with complicated ACD (%)	Patients with high validity reference test (%)
Articles not included in meta-analysis							
Laurell, 2006	Clinical evaluation	1,287	NR	NR	145 (11)	11 (8)	12 (1)
Toorenvliet, 2008	Clinical evaluation	802	NR	NR	44 (5)	6 (14)	41 (5)
Verbanck , 1989	US	123	NR	NR	52 (43)	8 (16)	10 (8)
Schwerk, 1993	US	130	58 (23-88)	66 (51)	52 (40)	13 (25)	24 (18)
Farag Soliman, 2004	US / CT	63	62 (median)	NR	43 (68)	20 (47)	34 (54)
Doringer, 1990	CT	33	71 (40-84)	20 (61)	21 (64)	2 (10)	9 (27)
Heverhagen, 2008	MRI	55	59 (29-76)	26 (47)	47 (85)	NR	16 (29)
Articles included in meta-analysis							
Cho, 1990	Barium enema / CT	56	63 (28-98)	37 (66)	27 (48)	16 (60)	22 (39)
Stefánsson, 1997	Barium enema / CT / laparoscopy	88	63 (29-91) (median)	64 (73)	52 (60)	NR	30 (34)
Zielke, 1997	US	143	56 (20-89)	79 (55)	74 (52)	11 (15)	32 (23)
Pradel, 1997	US / CT	64	64 (38-87)	NR	33 (52)	9 (27)	18 (33)
Hollerweger,2000	US	175	61 (15-89)	109 (62)	102 (58)	24 (24)	39 (23)
Rao, 1998	CT	150	59 (19-92)	91 (61)	64 (43)	13 (20)	41 (28)
Werner, 2003	CT	120	62 (21-88)	65 (54)	67 (56)	11 (16)	49 (41)
Tack, 2005	CT	110	57 (30-82)	70 (64)	39 (35)	14 (36)	74 (67)
Absolute number [π]		906					
Weighted average with CI			60.5 (58.4-62.6)	61 (57-66)	50 (44-56)	26 (18-36)	35 (25-46)
Patients pooled by CT		588	61.2 (58.7-63.6)	63 (57-69)	49 (41-56)	30 (18-44)	40 (27-52)
Patients pooled by US		382	60.3 (55.8-64.8)	59 (52-66)	55 (50-60)	21 (15-29)	23 (19-28)
Pooled US vs pooled CT			p=0.72	p=0.34	p=0.04	p=0.12	p<0.0001

Table 2 (continued): Independent variables extracted from prospective studies not included in meta-analysis dealing with diagnostic accuracy to diagnose acute colonic diverticulitis (ACD)

Study/year	Diagnostic modality	*n*	Mean age (range)	Women, *n* (%)	Participants with ACD (%)	Participants with complicated ACD (%)	Patients with high validity reference test (%)
Weighted average with CI			60.5 (58.4-62.6)	61 (57-66)	50 (44-56)	26 (18-36)	35 (25-46)
Patients pooled by CT		588	61.2 (58.7-3.6)	63 (57-69)	49 (41-56)	30 (18-44)	40 (27-52)
Patients pooled by US		382	60.3 (55.8-64.8)	59 (52-66)	55 (50-60)	21 (15-29)	23 (19-28)
Pooled US vs pooled CT			*p*=0.72	*p*=0.34	*p*=0.04	*p*=0.12	*p*<0.0001

ACD: acute colonic diverticulitis, defined as presence of both diverticula and bowel wall thickening

complicated ACD: complicated acute colonic diverticulitis, defined as presence of pericolic abscesses or signs of perforation or fistula

high validity reference test: a reference test in which the diagnosis ACD is confirmed by histopathological confirmation after surgery or colonoscopy with biopsy

NR: not reported

[π] As Pradel studied both US and CT in a head-to-head comparative study, the sum of the two pooled results does not match the total sum of absolute patients; the p-value between US and CT group is calculated by logistic regression estimating the proportion

Table 3: Alternative diagnoses in consecutive patients with clinically suspected acute colonic diverticulitis included in the meta-analysis

Study/year	Diagnostic modality	*n*	Participants with alternative diagnoses (%)	Participants with a specific alternative diagnosis (%)	Specific alternative diagnosis as first diagnosed by either US of CT (%)
Zielke, 1997	US	143	69 (48)	35 (24)	16 (46)
Hollerweger, 2000	US	175	73 (42)	47 (27)	NR
Cho, 1990	CT	56	29 (52)	23 (41)	20 (87)
Stefánsson, 1997	CT	88	36 (41)	24 (27)	NR
Pradel, 1997	US CT	64	31 (48)	24 (38)	12 (50) 8 (33)
Rao, 1998	CT	150	86 (57)	64 (43)	50 (78)
Werner, 2003	CT	120	53 (44)	31 (26)	22 (71)
Tack, 2005	CT	110	71 (65)	22 (20)	NR
Absolute number		906			
Weighted average (CI)			50 (44-56)	30 (25-36)	73 (59-85)
Patients pooled by CT		588	51 (44-59)	32 (24-40)	68 (47-86)
Patients pooled by US		382	45 (40-50)	28 (22-35)	48 (35-60)
Pooled US vs pooled CT [π]			*p*=0.04 (OR 1.31; CI: 1.012-1.697)	*p*=0.16	*p*=0.002 (OR 2.6; CI: 1.41-4.93)

NR: not reported
Alternative diagnoses are divided in specific alternative diagnosis clearly stated in the article and specific alternative diagnosis as first diagnosed by either US or CT
[π] the p-value between US and CT group is calculated by logistic regression estimating the proportion

Contrast Enema

Two studies reported on diagnostic accuracy of contrast enema in patients with suspected ACD that were eligible for inclusion. Both studies were of moderate quality and the number of patients was too small to permit a sensible meta-analysis.[15, 16] Reported sensitivities of contrast enema in these studies were 80%-83%, with a specificity of 81%-100%.

This systematic review has demonstrated that HRQoL and HS reach levels comparable to the general population after IPAA. It also illustrated that a systematic and uniform approach to QoL and its measurement is needed. Often in studies HS or HRQoL instruments were used while titles incorrectly referred to QoL.[12] QoL, HRQoL, and HS are different entities and are not interchangeable. Considering the HRQoL results in the high quality studies and the consistent results observed in the other studies, one might expect that QoL results in patients after IPAA for UC will be comparable to the general population as well. However, studies will have to be performed examining all the domains of QoL to answer this question.

To be able to improve future patient care, QoL evaluation is of importance. QoL is evaluated by assessing many more domains than HRQoL. This makes QoL questionnaires the most sensitive tool to detect subtle changes and flaws in today's patient care with regard to (HR)QoL. During the last decades, great advances have been made reducing mortality and decreasing morbidity which resulted in levels of HRQoL and HS comparable to the general population. Evaluating QoL and the separate domains can make further improvements possible for patients entrusted to us.

Discussion

Summary of results

The aim of this study was to systematically review the literature of the accuracy of the clinical evaluation and diagnostic modalities for patients with suspected ACD. In two-thirds of the patients the diagnosis of ACD can be made based on clinical evaluation without additional imaging.[6, 7] In one-third of the patients, additional imaging is a necessity to establish the diagnosis. US and CT are comparable in diagnosing diverticulitis and superior to other modalities. CT has the advantage of higher specificity and the ability to identify alternative diagnoses. The role of MRI is not yet clear in diagnosing ACD. Contrast enema should be considered an obsolete imaging technique to diagnose ACD based on lower sensitivity and specificity than US and CT.

Strengths and limitations of the study

Major strength of this study is the detailed evaluation of the literature and the study quality by applying the validated STARD model. This enabled us to give a clear and comprehensive overview of the quality and the possible risk of bias of the included studies. We could only pool the data of US and CT studies for meta-analysis. All studies included in the US and CT meta-analysis displayed acceptable homogeneity and were not affected by confounding. Although the studies reporting on diagnostic accuracy of US and CT were of acceptable overall quality, the lack of adequate reference testing to establish the final diagnosis was an important restriction in interpreting these studies. Histopathology is the gold standard for diagnostic studies of ACD. However, obtaining histological confirmation in the acute phase of uncomplicated ACD is seldom a real option because of the risk at colonoscopy and patient's discomfort. Selection of studies by stringent in- and exclusion criteria has introduced bias, for example by excluding studies that did not report a consecutive series of patients. However, including studies of methodological poor quality would have negatively affected the generalizability of meta-analysis results

Comparison with other studies

Based on results of this study, clinical evaluation should be considered the mainstay of the diagnostic process in ACD. This finding is in accordance with two recent reports in which

the use of a clinical (and laboratory) scoring system was analyzed to improve the clinical evaluation in patients suspected of having ACD.[21, 22] Such scoring systems are able to identify patients with ACD with a high degree of diagnostic accuracy without additional imaging, however only in a small subset of patients with pain solely in the lower left abdomen, the absence of vomiting and a CRP >50mg/l and only if there is no indication of complicated disease. These studies were not included in our systematic review since diagnostic accuracy was not calculated for each individual variable in terms of sensitivity or specificity.

An earlier meta-analysis by Laméris et al. regarding test accuracy of graded compression US and CT in diagnosing ACD showed comparable results to our study. Main difference is the finding of a significant difference in specificity favoring CT in our study. Differences in outcome results between the Laméris study and our meta-analysis are mainly attributed to a difference in quality assessment and more stringent inclusion criteria in our meta-analysis.[23] Based on results of these two meta-analyses, graded compression US seems safe and accurate in diagnosing ACD, with comparable sensitivity to CT.

A recent large prospective study of diagnostic accuracy in patients with acute abdominal pain supports this assumption. This study was designed to identify an optimal imaging strategy for the accurate detection of urgent conditions in patients with acute abdominal pain with ACD as second most common diagnosis (12% of the study population). A conditional strategy, with CT performed after inconclusive or negative US, resulted in the highest overall sensitivity and the lowest overall exposure to radiation in this study.[23]

This step-up approach seems a logical and safe approach for patients with suspected ACD and is supported by several findings in our study. The first step of the diagnostic process is an estimation of the probability of ACD based on clinical evaluation and laboratory findings. In case of questionable disease, an ultrasound examination is the following step. In case of an inconclusive or negative US, a CT scan is made.

Adoption of such a step-up approach is hampered by geographic differences and personal preferences in diagnosing ACD. In two surveys, conducted among colon- and rectal surgeons in the UK and USA, differences in the use of initial imaging techniques to diagnose ACD were clearly demonstrated. UK surgeons who deemed additional imaging necessary, chose US as the initial imaging technique in a third of patients as compared to only 7% of the colon- and rectal surgeons in the USA.[24, 25] Obesity might have been a reason why physicians favored initial CT over US. With approximately two-thirds of the population in various western parts of the world estimated as being overweight or obese the use of CT as initial screening for abdominal conditions is expected to increase further. Besides the well-known disadvantages of CT (i.e., exposure to radiation and contrast nephropathy), the reproducibility of CT images, and the ability to adequately define an alternative diagnosis, further aid in the widespread use of CT in diagnosing ACD.

Furthermore, CT has the advantage of delineating the extent of the extra luminal disease process and may also direct therapeutic intervention in case of complicated disease, e.g., percutaneous drainage of intra-abdominal abscesses.[26, 27]

Liberal use of CT in patients suspected of uncomplicated diverticulitis, however, is not recommended because in 90% of the patients with ACD the disease follows a rather indolent course.[28] Furthermore, it has been shown that cross-sectional imaging in patients with suspected ACD only leads to alterations in management in 7% of the patients, with the majority being minor changes.[6]

The step-up approach does not apply for critically ill patients with acute abdominal pain and signs of sepsis, possibly caused by complicated diverticulitis. These patients need to be subjected to immediate CT scanning without further delay to initiate proper treatment.[29, 30]

Implications for clinical practice

Although imaging is widely applied in patients suspected of ACD, not every patient needs the complete diagnostic work-up. Despite the fact that we are able to diagnose two-thirds of the patients with suspected ACD based on clinical evaluation alone, we fail to define this group of patients. The CRP may be an important factor in identifying patients with complicated ACD. In a recently published report a CRP level over 90mg/l was 88% sensitive and 75% specific for complicated disease in patients not on corticosteroids. A CRP level below 50mg/l at hospital admission correlated with non-complicated diverticulitis, suggesting that CT may be avoided in patients presenting with this level of CRP.[31] The contribution of a single variable or a combination of variables to diagnose ACD should be further researched in a prospective trial to identify patients who may be safely withheld from further diagnostics in the acute phase to diagnose diverticulitis. It remains of key importance to recognize those patients with signs of complicated disease, who are in need of early intervention.

The step-up approach of diagnosing ACD presented in this review might be a first step in reducing patient's burden and risks, while controlling costs through a more efficient use of resources.

Reference list

1 Rafferty J., Shellito P., Hyman N. H., Buie W. D., and Standards Committee of American Society of Colon and Rectal Surgeons, 2006, "Practice parameters for sigmoid diverticulitis", Dis Colon Rectum, 49(7), p. 939-44.

2 Etzioni D. A., Mack T. M., Beart R. W., and Kaiser A. M., 2009, "Diverticulitis in the United States: 1998-2005: changing patterns of disease and treatment", Ann Surg, 249(2), p. 210-7.

3 Broderick-Villa G., Burchette R. J., Collins J. C., Abbas M. A., and Haigh P. I., 2005, "Hospitalization for acute diverticulitis does not mandate routine elective colectomy", Arch Surg, 140(6), p. 576-81; discussion 581-3.

4 Chapman J. R., Dozois E. J., Wolff B. G., Gullerud R. E., and Larson D. R., 2006, "Diverticulitis: a progressive disease? Do multiple recurrences predict less favorable outcomes?", Ann Surg, 243(6), p. 876-830; discussion 880-3.

5 Bossuyt P. M., Reitsma J. B., Bruns D. E., Gatsonis C. A., Glasziou P. P., Irwig L. M., Lijmer J. G., Moher D., Rennie D., de Vet H. C., and Standards for Reporting of Diagnostic Accuracy, 2003, "Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative", Clin Radiol, 58(8), p. 575-80.

6 Toorenvliet B. R., Bakker R. F., Breslau P. J., Merkus J. W., and Hamming J. F., 2010, "Colonic diverticulitis: a prospective analysis of diagnostic accuracy and clinical decision-making", Colorectal Dis, 12(3), p. 179-86.

7 Laurell H., Hansson L. E., and Gunnarsson U., 2007, "Acute diverticulitis--clinical presentation and differential diagnostics", Colorectal Dis, 9(6), p. 496-501; discussion 501-2.

8 Verbanck J., Lambrecht S., Rutgeerts L., Ghillebert G., Buyse T., Naesens M., and Tytgat H., 1989, "Can sonography diagnose acute colonic diverticulitis in patients with acute intestinal inflammation? A prospective study", J Clin Ultrasound, 17(9), p. 661-6.

9 Schwerk W. B., Schwarz S., and Rothmund M., 1992, "Sonography in acute colonic diverticulitis. A prospective study", Dis Colon Rectum, 35(11), p. 1077-84.

10 Farag Soliman M., Wüstner M., Sturm J., Werner A., Diehl S. J., Düber C., and Post S., 2004, "[Primary diagnostics of acute diverticulitis of the sigmoid]", Ultraschall Med, 25(5), p. 342-7.

11 Zielke A., Hasse C., Nies C., Kisker O., Voss M., Sitter H., and Rothmund M., 1997, "Prospective evaluation of ultrasonography in acute colonic diverticulitis", Br J Surg, 84(3), p. 385-8.

12 Hollerweger A., Macheiner P., Rettenbacher T., Brunner W., and Gritzmann N., 2001, "Colonic diverticulitis: diagnostic value and appearance of inflamed diverticula-sonographic evaluation", Eur Radiol, 11(10), p. 1956-63.

13 Pradel J. A., Adell J. F., Taourel P., Djafari M., Monnin-Delhom E., and Bruel J. M., 1997, "Acute colonic diverticulitis: prospective comparative evaluation with US and CT", Radiology, 205(2), p. 503-12.

14 Doringer E., and Ferner R., 1990, "[Computed tomography of colonic diverticulitis]", Rofo, 152(1), p. 76-9.

15 Cho K. C., Morehouse H. T., Alterman D. D., and Thornhill B. A., 1990, "Sigmoid diverticulitis: diagnostic role of CT--

comparison with barium enema studies", Radiology, 176(1), p. 111-5.

16 Stefánsson T., Nyman R., Nilsson S., Ekbom A., and Påhlman L., 1997, "Diverticulitis of the sigmoid colon. A comparison of CT, colonic enema and laparoscopy", Acta Radiol, 38(2), p. 313-9.

17 Rao P. M., Rhea J. T., Novelline R. A., Dobbins J. M., Lawrason J. N., Sacknoff R., and Stuk J. L., 1998, "Helical CT with only colonic contrast material for diagnosing diverticulitis: prospective evaluation of 150 patients", AJR Am J Roentgenol, 170(6), p. 1445-9.

18 Werner A., Diehl S. J., Farag-Soliman M., and Düber C., 2003, "Multi-slice spiral CT in routine diagnosis of suspected acute left-sided colonic diverticulitis: a prospective study of 120 patients", Eur Radiol, 13(12), p. 2596-603.

19 Tack D., Bohy P., Perlot I., De Maertelaer V., Alkeilani O., Sourtzis S., and Gevenois P. A., 2005, "Suspected acute colon diverticulitis: imaging with low-dose unenhanced multi-detector row CT", Radiology, 237(1), p. 189-96.

20 Heverhagen J. T., Sitter H., Zielke A., and Klose K. J., 2008, "Prospective evaluation of the value of magnetic resonance imaging in suspected acute sigmoid diverticulitis", Dis Colon Rectum, 51(12), p. 1810-5.

21 Andeweg C. S., Knobben L., Hendriks J. C., Bleichrodt R. P., and van Goor H., 2011, "How to Diagnose Acute Left-sided Colonic Diverticulitis: Proposal for a Clinical Scoring System", Ann Surg, 253(5), p. 940-6.

22 Laméris W., van Randen A., van Gulik T. M., Busch O. R., Winkelhagen J., Bossuyt P. M., Stoker J., and Boermeester M. A., 2010, "A clinical decision rule to establish the diagnosis of acute diverticulitis at the emergency department", Dis Colon Rectum, 53(6), p. 896-904.

23 Laméris W., van Randen A., van Es H. W., van Heesewijk J. P., van Ramshorst B., Bouma W. H., ten Hove W., van Leeuwen M. S., van Keulen E. M., Dijkgraaf M. G., Bossuyt P. M., Boermeester M. A., Stoker J., and OPTIMA study group, 2009, "Imaging strategies for detection of urgent conditions in patients with acute abdominal pain: diagnostic accuracy study", BMJ, 338, p. b2431.

24 Munikrishnan V., Helmy A., Elkhider H., and Omer A. A., 2006, "Management of acute diverticulitis in the East Anglian region: results of a United Kingdom regional survey", Dis Colon Rectum, 49(9), p. 1332-40.

25 Schechter S., Mulvey J., and Eisenstat T. E., 1999, "Management of uncomplicated acute diverticulitis: results of a survey", Dis Colon Rectum, 42(4), p. 470-5; discussion 475-6.

26 Ambrosetti P., Becker C., and Terrier F., 2002, "Colonic diverticulitis: impact of imaging on surgical management -- a prospective study of 542 patients", Eur Radiol, 12(5), p. 1145-9.

27 Ambrosetti P., 2008, "Acute diverticulitis of the left colon: value of the initial CT and timing of elective colectomy", J Gastrointest Surg, 12(8), p. 1318-20.

28 Schug-Pass C., Geers P., Hügel O., Lippert H., and Köckerling F., 2010, "Prospective randomized trial comparing short-term antibiotic therapy versus standard therapy for acute uncomplicated sigmoid diverticulitis", Int J Colorectal Dis, 25(6), p. 751-9.

29 Andeweg C. S., Mulder I. M., Felt-Bersma R. J., Verbon A., van der Wilt G. J., van Goor H., Lange J. F., Stoker J., Boermeester M. A., and Bleichrodt R. P., 2013, "Guidelines of Diagnostics and Treatment of Acute Left-

Sided Colonic Diverticulitis", Dig Surg, 30(4-6), p. 278-292.

30 Dellinger R. P., Levy M. M., Rhodes A., Annane D., Gerlach H., Opal S. M., Sevransky J. E., Sprung C. L., Douglas I. S., Jaeschke R., Osborn T. M., Nunnally M. E., Townsend S. R., Reinhart K., Kleinpell R. M., Angus D. C., Deutschman C. S., Machado F. R., Rubenfeld G. D., Webb S. A., Beale R. J., Vincent J. L., Moreno R., and Pediatric Subgroup, 2013, "Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012", Crit Care Med, 41(2), p. 580-637.

31 Nizri E., Spring S., Ben-Yehuda A., Khatib M., Klausner J., and Greenberg R., 2013, "C-reactive protein as a marker of complicated diverticulitis in patients on anti-inflammatory medications", Tech Coloproctol.

Table S1: Search strategy for electronic databases

[Diverticulitis (MeSH) OR Colonic diverticulitis (MeSH)] AND clinical diagnosis OR diagnostic accuracy OR Contrast Enema OR Barium Enema OR contrast barium enema OR double contrast barium enema OR “Ultrasonography” (MeSH) OR ultrasound OR ultrasound diagnosis OR “Tomography, Spiral Computed” (MeSH) OR “Tomography, X-Ray Computed” (MeSH) OR “Tomography Scanners, X-Ray Computed” (Mesh) OR “Magnetic Resonance Imaging” (Mesh) OR “Colonography, Computed Tomographic” (Mesh) AND prospective studies [mh] or control * [tw] OR prospectiv*

Table S2: Quality assessment of included studies based on the STARD initiative checklist

Study / year	Diagnostic accuracy (1)	Aim of the study (2)	Study population (3)	Participant recruitment (4)	Participant sampling (5)	Data collection (6)	Reference standard (7)	Technical specifications (8)
Contrast Enema								
Cho, 1990	Study presents sensitivity and specificity of	Assessment of diagnostic accuracy of CT and BE in hospitalized patients	Patients with the presumptive diagnosis ACD based on patient history, physical examination and strict criteria were: ≥3 of the following findings: left lower quadrant abdominal pain; temp >37.3 C; rebound tenderness and WBCC >10,000/mm3 *n*=56 single institution USA, 1990	Participants were recruited based on presenting symptoms	Consecutive series of participants	Prospective	High validity reference test is a test by histopathological confirmation (after surgery or colonoscopy with biopsy) Low validity reference test is a test by clinical outcome possibly supported by examinations other than the index test	BE was done as single-contrast study Glucagon administration at discretion of radiologist Non-helical CT Lower abdomen 10x10 mm (when the lower abdomen showed no diverticulitis the upper abdomen was scanned as well) Iv contrast in 50% Standard oral and rectal contrast Air insufflation in 77% of patients
Stefánsson, 1997	Study presents sensitivity and specificity of	Evaluate use of laparoscopy, CT, colonic enema and laboratory tests in diagnosing diverticulitis of the sigmoid colon	Acute lower pain with suspicion of diverticulitis based on history, physical examination and laboratory tests *n*=88 single institution Sweden, 1997	Participants were recruited based on presenting symptoms	Consecutive series of participants	Prospective	High validity reference test is a test by histopathological confirmation (after surgery or colonoscopy with biopsy) Low validity reference test is a test by clinical outcome possibly supported by examinations other than the index test	BE was done without bowel preparation, single contrast technique using barium Helical, multislice CT Upper abdomen 8x12mm, lower abdomen 8x8mm Iv contrast 100ml, rate 3ml/s and 40s delay Oral contrast 800ml Rectal air insufflation Laparoscopy performed by the same colorectal surgeon, 10mm trocart umbilicus, 5mm right fossa
Ultrasound								
Verbanck , 1989	Study presents sensitivity and specificity	Assessment of the value of ultrasonography in diagnosing ACD	Clinical signs of acute intestinal inflammation Lower abdominal pain, fever, abdominal distention and rebound tenderness *n*=123 single institution, Belgium, 1998	Participants were recruited based on presenting symptoms	Consecutivity not mentioned	Prospective	High validity reference test is a test by histopathological confirmation (after surgery or colonoscopy with biopsy) Low validity reference test is a test by clinical outcome possibly supported by examinations other than the index test	Linear and curved probe 3.5 – MHz Graded compression

Table S2: Quality assessment of included studies based on the STARD initiative checklist

Study / year	Diagnostic accuracy (1)	Aim of the study (2)	Study population (3)	Participant recruitment (4)	Participant sampling (5)	Data collection (6)	Reference standard (7)	Technical specifications (8)
Schwerk, 1992	Study presents sensitivity and specificity	Assessment of ultrasonography for the diagnosis of acute and complicated colonic diverticulitis	Patients with the admitting diagnosis of suspected ACD or with abdominal complaints because of which the disease entered into differential consideration Patients were categorized according to suspicion of ACD *n*=130 Single institution Germany, 1992	Participants were recruited based on presenting symptoms	Consecutivity not mentioned	Prospective	High validity reference test is a test by histopathological confirmation (after surgery or colonoscopy with biopsy) Low validity reference test is a test by clinical outcome possibly supported by examinations other than the index test	Linear and curved probe 3.5 – MHz Graded compression
Zielke, 1997	Study presents sensitivity and specificity	Assessment of diagnostic accuracy and clinical value of US by surgical residents	Inclusion of patients with suspected ACD based on history, physical examination and laboratory findings not further specified *n*=143 single institution Germany, 1997	Participants were recruited based on presenting symptoms	Consecutive series of participants	Prospective	High validity reference test is a test by histopathological confirmation (after surgery or colonoscopy with biopsy) Low validity reference test is a test by clinical outcome possibly supported by examinations other than the index test	Linear and curved probe frequency 3.5 – 5 MHz graded compression
Hollerweger, 2001	Study presents sensitivity and specificity	Assessment of diagnostic accuracy of US and investigate sonographic appearance and detectablity of inflamed diverticula	Inclusion of patients with suspected ACD based on history, physical examination and laboratory findings not further specified *n*=175 single institution Austria	Participants were recruited based on presenting symptoms	Consecutive series of participants	Prospective	High validity reference test is a test by histopathological confirmation (after surgery or colonoscopy with biopsy) Low validity reference test is a test by clinical outcome possibly supported by examinations other than the index test	Linear and curved probe frequency 2-4 MHz and 4-7 or 5-10 MHz Graded compression
Ultrasound vs Computed Tomography								
Pradel, 1997	Study presents sensitivity and specificity	Comparison of diagnostic accuracy of US versus CT	Inclusion of patients with suspected ACD based on history, physical and laboratory findings not further specified *n*=64 single institution France, 1997	Participants were recruited because of their presenting symptoms	Consecutive series of participants	Prospective	High validity reference test is a test by histopathological confirmation (after surgery or colonoscopy with biopsy) Low validity reference test is a test by clinical outcome possibly supported by examinations other than the index test	linear and curved probe frequency 5-10 and 2-4 MHz graded compression Non helical, upper abdomen 8x12-16mm and lower abdomen 8x8mm Iv contrast 88% and oral 64%

Table S2: Quality assessment of included studies based on the STARD initiative checklist

Study / year	Diagnostic accuracy (1)	Aim of the study (2)	Study population (3)	Participant recruitment (4)	Participant sampling (5)	Data collection (6)	Reference standard (7)	Technical specifications (8)
Farag Soliman, 2004	Study presents sensitivity and specificity	Comparison of diagnostic accuracy of US vs CT	Inclusion of patients with suspected ACD based on history, physical and laboratory findings not further specified n=63 single institution Germany, 2004	Participants were recruited because of their presenting symptoms	No consecutive series In case of no availability of US <24 hours patients were not included in the study	Prospective	High validity reference test is a test by histopathological confirmation (after surgery or colonoscopy with biopsy) Low validity reference test is a test by clinical outcome possibly supported by examinations other than the index test	Linear and curved probe 6-10 MHz and 3.5-6 MHz Graded compression Helical, multi-slice CT, abdomen 5x7mm and 5x5mm Iv contrast (100ml) and rectal contrast (1000ml)
Computed Tomography								
Doringer, 1990	Study presents sensitivity and specificity	The assessment of diagnostic accuracy of CT and the predictive value of CT symptoms	Inclusion of patients with suspected ACD based on history, physical and laboratory findings specified in lower abdominal pain, leucocytose and elevation of BSE *n*=33 single institution Germany, 1990	Participants were recruited because of their presenting symptoms	No consecutive series	Prospective	High validity reference test is a test by histopathological confirmation (after surgery or colonoscopy with biopsy) Low validity reference test is a test by clinical outcome possibly supported by examinations other than the index test	Non helical CT CT protocol not further specified Iv and rectal contrast but not further specified
Rao, 1998	Study presents sensitivity and specificity	The assessment of diagnostic accuracy of CT (with colonic contrast material only)	Inclusion of patients with the presumptive diagnosis of ACD based on patient history; physical examination and strict criteria were: ≥2 of the following findings: abdominal pain; anorexia; nausea; vomiting; temp>37.5C; rebound tenderness; guarding; WBCC < 10,000/mm3 *n*=150 single institution USA, 1998	Participants were recruited because of their presenting symptoms	Consecutive series of participants	Prospective	High validity reference test is a test by histopathological confirmation (after surgery or colonoscopy with biopsy) Low validity reference test is a test by clinical outcome possibly supported by examinations other than the index test	Helical CT Abdomen 5x7.5mm Iv contrast 2% and rectal contrast 100% (1000ml)

Table S2: Quality assessment of included studies based on the STARD initiative checklist

Study / year	Diagnostic accuracy (1)	Aim of the study (2)	Study population (3)	Participant recruitment (4)	Participant sampling (5)	Data collection (6)	Reference standard (7)	Technical specifications (8)
Werner, 2003	Study presents sensitivity and specificity	The assessment of diagnostic accuracy of CT	Inclusion of patients with the presumptive diagnosis of ACD based on patient history; physical examination and laboratory findings Left lower abdominal pain and CRP >5mg/l *n*=120 single institution Germany, 2003	Participants were recruited because of their presenting symptoms	Consecutive series of participants	Prospective	High validity reference test is a test by histo-pathological confirmation (after surgery or colonoscopy with biopsy) Low validity reference test is a test by clinical outcome possibly supported by examinations other than the index test	Helical, multislice CT from the pelvic floor to the lower edge of the liver was performed 4x2.5mm Iv contrast 100% (1.3 ml/kg) If initial scan didn't show ACD the upper abdomen was scanned as well
Tack, 2005	Study presents sensitivity and specificity	The study compared accuracy of two different CT regimes, contrast enhanced and standard dose CT (120mAs) versus no contrast low dose CT (30mAs)	Inclusion of patients with the presumptive diagnosis of ACD (pain in the left iliac fossa for less than 2 weeks) *n*=110 single institution Belgium, 2005	Participants were recruited because of their presenting symptoms	Consecutive series of participants	Prospective	High validity reference test is a test by histopathological confirmation (after surgery or colonoscopy with biopsy) Low validity reference test is a test by clinical outcome possibly supported by examinations other than the index test	Helical, multislice CT Abdomen 4x2.5mm Two different CT regimes to compare contrast enhanced and standard dose CT (120 mAs) versus no contrast low dose CT (30mAs)
MRI								
Heverhagen, 2008	Study presents sensitivity and specificity	The assessment of diagnostic accuracy of MRI	Inclusion of patients with the presumptive diagnosis of ACD (lower left quadrant pain and localized peritonitis) Specified in symptoms per patient (pain, WBCC, fever, vomiting, rebound tenderness) *n*=55 single institution Germany, 2008	Participants were recruited because of their presenting symptoms	Consecutive series of participants	Prospective	High validity reference test is a test by histopathological confirmation (after surgery or colonoscopy with biopsy) Low validity reference test is a test by clinical outcome possibly supported by examinations other than the index test	1.0 T MR scanner using a body phased-array coil immediately before MRI scopolamine was administered to reduce bowel peristalsis

Table S2: Quality assessment of included studies based on the STARD initiative checklist

Study / year	Diagnostic accuracy (1)	Aim of the study (2)	Study population (3)	Participant recruitment (4)	Participant sampling (5)	Data collection (6)	Reference standard (7)	Technical specifications (8)
Clinical diagnosis								
Laurell , 2006	Study presents sensitivity and specificity of clinical diagnosis diverticulitis	Describe clinical presentation of acute diverticulitis in an emergency department and compare to non-specific abdominal pain (NSAP)	Patients with acute abdominal pain of up to 7 days older than 1 year of age *n*=3073 single institution Sweden, 2006	Participants were recruited based on presenting symptoms and laboratory findings	No consecutive patient recruitment mentioned Complete follow-up 92%	Prospective	Abdominal pain, fever and/or elevation of CRP and a finding of diverticula at X-ray or endoscopic examination prior to admission or during follow-up. For statistical analysis diagnosis at one year follow-up were used and describes those patients who actually had diverticulitis	The attending physician had to suggest a first and second most likely diagnosis
Toorenvliet, 2008	Study presents sensitivity and specificity of clinical diagnosis diverticulitis	Evaluate the diagnostic accuracy of clinical evaluation and imaging modalities such as US and CT and determine the value of these examinations in clinical decision making	Patients with acute abdominal pain evaluated at the ED by a surgeon *n*=802 single institution The Netherlands, 2008	Participants were recruited based on presenting symptoms and laboratory findings	Consecutive series of participants	Prospective	Pathological examination for patients who were operated and clinical response to medical therapy with an adequate follow-up for those that were managed conservatively	Clinical diagnosis based on history, physical examination and blood and urine analysis with a subsequent management proposal, after that a decision was made whether or not to perform additional imaging, US or CT at the radiologist discretion

STARD initiative checklist
(1) Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').
(2) State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.
(3) The study population: The inclusion and exclusion criteria, setting and locations where data were collected.
(4) Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that participants had received the index tests or the reference standard?
(5) Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.
(6) Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?
(7) The reference standard and its rationale.
(8) Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.

Table S2: Quality assessment of included studies based on the STARD initiative checklist (continued)

Study / year	Definition indextest (9)	Persons and Expertise (10)	Blinding (11)	Measures of diagnostic accuracy (12)	Test Reproducibility (13)	Study date and duration (14)	Demographics study population (15)
Contrast Enema							
Cho, 1990	BE: (a) extravasation of barium or air, (b) segmental narrowing with thickened and tethered mucosa or (c) extraluminal mass effect CT: Pericolic fat inflammation with bowel wall thickening >4-5 mm	One of four radiologists (CT) or GI-radiologists (BE)	No blind evaluation between reference and index test No independent evaluation of indextest since patients were referred to the radiological department and the radiologist knew the presumptive diagnosis of ACD	Sensitivity and specificity were enucleated in the study and PPV, NPV, positive LR, negative LR and their 95% CI can be subsequently calculated	No methods for calculating test reproducibility	1986-1989 Study period 36 months	Final diagnosis ACD *n*=27 mean age 63, proportion females 66%, abscesses 29%, fistulas 0%, surgery 20%, co-morbidity and current treatments were not specified patients were recruited at the ER
Stefánsson, 1997	BE: narrowing in the bowel lumen with an irregularity of the mucosa or a leakage of contrast material outside the lumen of the bowel combined with diverticulosis CT: Pericolic fat inflammation with bowel wall thickening <4-5mm and diverticula Laparoscopy: Reddened, inflamed and edematous serosa through the laparoscope, and thickenend bowel wall identified through palpating with an instrument, inflamed adhesions to adjacent organs or abdominal wall	CE: persons and expertise not given CT: separately interpreted by two experienced radiologist, diagnosis was consensus between the radiologists Laparoscopy: same colorectal surgeon, experience not mentioned	CT interpretation was done separately between two radiologists blinded to the results of clinical assessment, laboratory tests, CE and laparoscopy CE and laparoscopy blinding not mentioned	Sensitivity and specificity were enucleated in the study and PPV, NPV, positive LR, negative LR and their 95% CI can be subsequently calculated	No methods for calculating test reproducibility	November 1991 – April 1994 Study period 40 months	Final diagnosis ACD *n*=52 mean age 63, proportion females 73%, co-morbidity and current treatments were not specified patient recruitment not clearly specified
Ultrasound							
Verbanck , 1989	Diffuse, hypoechoic bowel wall thickening of more than 4mm over at least a 5cm long bowel loop in the left hemi abdomen	Persons and expertise interpreting US findings not specified	Sonographic investigator was not given information regarding clinical diagnosis or previous history, but was informed only about the presenting symptoms	Sensitivity and specificity were enucleated in the study and PPV, NPV, positive LR, negative LR and their 95% CI can be subsequently calculated	No methods for calculating test reproducibility	Study period 24 months Exact date not given	Final diagnosis ACD *n*=52 mean age not reported, proportion females not reported, abscesses 16%, fistulas 4%, co-morbidity and current treatments were not specified patient recruitment not clearly specified

Table S2: Quality assessment of included studies based on the STARD initiative checklist (continued)

Study / year	Definition indextest (9)	Persons and Expertise (10)	Blinding (11)	Measures of diagnostic accuracy (12)	Test Reproducibility (13)	Study date and duration (14)	Demographics study population (15)
Schwerk, 1992	Sonographic visualization of a predominantly hypoechogenic thickened segment of the colon presenting with pain on graded compression, hyperechoic diverticula, and a surrounding rigid zone of increased echogenicity thickness of the bowelwall was assessed by measuring the maximum wall diameter of that colon segment	Ultrasound done by authors, experience not further specified	Sonographic investigator had knowledge of the patient being a diverticulitis study patient, but was blinded to details of the clinical examination	Sensitivity and specificity were enucleated in the study and PPV, NPV, positive LR, negative LR and their 95% CI can be subsequently calculated, clearly stated in evaluation and calculations	No methods for calculating test reproducibility	Study period 24 months Exact date not given	Final diagnosis ACD *n*= 52 mean age 58, proportion females 51%, abscesses 16%, fistulas 4%, co-morbidity and current treatments were not specified patient recruitment not clearly specified *n*=2 patients with diverticulitis of the coecum and tranversum
Zielke, 1997	Visualization of a hypoperistaltic segment with hypoechogenic mural thickening	11 different surgeons in training who passed a 3 month rotation in the surgical sonography department	No blind evaluation between index test and reference test Independent evaluation of index test since patients were referred to an arbitrarily chosen surgeon not involved in details of clinical evaluation.	TP/TN/FP/FN are given, sensitivity and specificity, NPV, PPV, LR+ and LR- with 95% CI are calculated	No methods for calculating test reproducibility	No exact date given but prior to 1997 Study period 48 months	Final diagnosis ACD *n*=74, mean age 56, proportion females 55%, abscesses 8%, fistulas 2%, surgery 22% co-morbidity and current treatments were not specified patients were recruited at the ER
Hollerweger, 2001	Segmental bowel wall thickening of ≥5mm Pericolic inflammation Inflamed divderticula or evidence of complicated disease (perforations, abscesses, fistulas)	One of four radiologists experienced in gastrointestinal sonography	No blind evaluation between index test and reference test since patients were referred to the radiological department and the radiologist knew the presumptive diagnosis of ACD	Sensitivity and specificity were enucleated in the study and PPV, NPV, positive LR, negative LR and their 95% CI can be subsequently calculated	Control group of 40 patients without clinical suspicion of ACD underwent US to evaluate the appearance of non-inflamed diverticula	January 1998 to May 2000 Study period 27	Final diagnosis ACD *n*=102 mean age 61, proportion females 62%, abscesses 11%, fistulas 6%, perforations 7%, surgery % co-morbidity and current treatments were not specified; patient recruitment unclear

Table S2: Quality assessment of included studies based on the STARD initiative checklist (continued)

Study / year	Definition indextest (9)	Persons and Expertise (10)	Blinding (11)	Measures of diagnostic accuracy (12)	Test Reproducibility (13)	Study date and duration (14)	Demographics study population (15)
US vs CT							
Pradel ,1997	Four criteria: Thickening of the bowel wall more than 4mm Identification of diverticula Inflammatory pericolonic fat Pericolic abscess in case of complicated diverticulitis	Two of five >3-5 years experience in GI radiology radiologists	The radiologists were blinded to the result of the other imaging examination. As the tests in this study were both index tests and not reference tests for another, no formal blinding was applied between index and reference test No independent evaluation of index test since patients were referred to the radiological department with the radiologist knowing the presumptive diagnosis ACD	TP/TN/FP/FN are given, sensitivity and specificity, NPV, PPV, LR+ and LR- with 95% CI are calculated	Intrareader and interreader agreements (Cohen kappa statistic)	August 1994 – April 1996 Study period 20 months	Final diagnosis ACD *n*=33, mean age 64 proportion females NR, spectrum of presenting symptoms 75% WBC >10; 78% temp >37.5 C free perforations 3% contained perforations 3% abscesses 14%, fistulas NR surgery 34% (mean 63 days after presentation) co-morbidity and current treatment were not specified patients were referred to the imaging department on the basis of clinician's judgment
Farag Soliman, 2004	Pericolic fat inflammation with bowel wall thickening >5mm	Four experienced researchers with a focus on gastrointestinal disorders, not further specified	The researcher were blinded to the result of the other imaging examination	TP/TN/FP/FN are given, sensitivity and specificity, NPV, PPV, LR+ and LR- with 95% CI are calculated	No methods for calculating test reproducibility	Study period 16 months Exact date not given	Final diagnosis ACD *n*=43 Median age 62, proportion females not reported, complicated diverticulitis *n*=20 co-morbidity and current treatments were not specified patients were admitted to the hospital
CT							
Doringer, 1990	Pericolic fat inflammation with bowel wall thickening >4mm and the presence of diverticula Pericolic abscess in case of complicated diverticulitis	Persons and expertise interpreting CT findings not specified	Not mentioned No blind evaluation between reference test and index test	TP/TN/FP/FN are given, sensitivity and specificity, NPV, PPV, LR+ and LR- with 95% CI are calculated	No methods for calculating test reproducibility	January 1988 to March 1989 Study period months 13	Final diagnosis ACD *n*=21 (64%) Median age 71, proportion females 61%, complicated diverticulitis *n*=2 (10%) co-morbidity and current treatments were not specified patient recruitment unclear

Table S2: Quality assessment of included studies based on the STARD initiative checklist (continued)

Study / year	Definition indextest (9)	Persons and Expertise (10)	Blinding (11)	Measures of diagnostic accuracy (12)	Test Reproducibility (13)	Study date and duration (14)	Demographics study population (15)
Rao, 1998	Pericolic fat inflammation with bowel wall thickening >5mm and the presence of diverticula Pericolic abscess, air bubbles, free fluid and fistula in case of complicated diverticulitis	Two experienced radiologists	No blind evaluation between reference test and index test	TP/TN/FP/FN are given, sensitivity and specificity, NPV, PPV, LR+ and LR- with 95% CI are calculated	No methods for calculating test reproducibility	June 1996 to September 1997 Study period 15 months	Final diagnosis ACD *n*=64 Median age 59, proportion females 61%, complicated diverticulitis *n*=13 (20%) co-morbidity and current treatments were not specified patients were recruited at the hospital ER
Werner, 2003	Pericolic fat inflammation with bowel wall thickening >4mm and the presence of diverticula Contained or free perforation or abscess, in case of complicated diverticulitis	Immediately interpretation by radiologist on call Final diagnosis made by two experienced radiologists in consensus within 8 h	No blind evaluation between reference test and index test	TP/TN/FP/FN are given, sensitivity and specificity, NPV, PPV, LR+ and LR- with 95% CI are calculated	No methods for calculating test reproducibility	Study period 15 months Exact date not given, but before 2002	Final diagnosis ACD *n*=67 (56%) Median age 62, proportion females 54%, complicated diverticulitis *n*=11 (16%) co-morbidity and current treatments were not specified patients were recruited at the hospital ER
Tack, 2005	Pericolic fat inflammation with bowel wall thickening not further specified (the radiologist had to give the wall thickness in mm) and the low grade diverticulitis or high grade diverticulitis according to the Ambrosetti criteria (abscess formation, gaseous collection and or fistula in case of complicated ACD)	Four readers; 1 general radiologist with >20 yrs experience; 1 GE radiologist >10 yrs experience; 1 radiologist in training; 1 gastroenterologist	The radiologists were blinded to the result of the other examination (two different CT regimes). These tests were both indextests, thus no formal blind evaluation between reference and index test was applies	TP/TN/FP/FN are given, sensitivity and specificity, NPV, PPV, LR+ and LR- with 95% CI are calculated	Definitive diagnosis of ACD was established by two radiologists and one gastroenterologist, intrareader and interreader agreements (Cohen kappa statistic) and logistic regression were used to model the probability of correctly diagnosing ACD as a function of different CT signs	February to August 2002 Study period 6 months	Final diagnosis ACD *n*=39 (35%) Median age 57, proportion females 64%, complicated diverticulitis *n*=14 (36%) co-morbidity and current treatments were not specified patient recruitment unclear

Table S2: Quality assessment of included studies based on the STARD initiative checklist (continued)

Study / year	Definition indextest (9)	Persons and Expertise (10)	Blinding (11)	Measures of diagnostic accuracy (12)	Test Reproducibility (13)	Study date and duration (14)	Demographics study population (15)
MRI							
Heverhagen, 2008	Presence of at least one diverticulum, colonic wall thickening (>5mm) and pericolic fatty infiltration. Supportive of the diagnosis were segmental narrowing, ascites and abscesses	Evaluation by two assessors, experience not further specified	The radiologists were blinded to all clinical, laboratory and radiologic results, as well as the results of each other, but aware of the study design	TP/TN/FP/FN are given, sensitivity and specificity, NPV, PPV, LR+ and LR- with 95% CI are calculated	No methods for calculating test reproducibility	Study period is not given	Final diagnosis ACD *n*=47 (85%) Median age 59, proportion females 47%, complicated diverticulitis only mentioned based on MRI findings and differs significantly between two assessors (9% vs 34%) co-morbidity and current treatments were not specified patient recruitment on emergency department by an experienced surgeon
Clinical diagnosis							
Laurell, 2006	Detailed schedule for history, clinical signs and results of laboratory investigations. Suggestion of attending physician first and second most likely diagnosis	Attending physician, not further specified	No blind evaluation between index test and reference test One year after clinical diagnosis final diagnosis was established, final diagnosis based on clinical parameters and X-ray or endoscopic examination, not mentioned who decides about final diagnosis	Sensitivity and specificity are given of preliminary diagnosis at the emergency department and discharge diagnosis when patients were hospitalized	Not done	February 1st 1997 to 1st of June 2000 Study period 41 months	Final diagnosis ACD *n*=145 mean age 62, proportion females 65% 37% left abdominal tenderness only, 14% vomiting as compared to 27% NSAP (p<0.001) 54% previous episodes as compared to 40% NSAP (p<0.001) CRP 73 as compared to 20 NSAP (p<0.001)
Toorenvliet, 2008	Clinical diagnosis with additional imaging if deemed necessary	84% of patients were evaluated at the ED by surgical residents in their first 3 years of training, other by senior residents of surgeons	No blind evaluation between index test and reference test	TP/TN/FP/FN are given, sensitivity and specificity, NPV, PPV, LR+ and LR-	Not done	June 2005 and July 2006 Study period 12 months	First clinical diagnosis ACD *n*=60, final diagnosis *n*=57 14 of the 57 patients with ACD as final diagnosis were not suspected of having ACD as the initial diagnosis

STARD initiative checklist
(9) Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.
(10) The number, training and expertise of the persons executing and reading the index tests and the reference standard.
(11) Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.
(12) Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).
(13) Methods for calculating test reproducibility, if done.
(14) When study was performed, including beginning and end dates of recruitment.
(15) Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms, comorbidity, current treatments, recruitment centers).

Table S2: Quality assessment of included studies based on the STARD initiative checklist (continued II)

Study / year	Percentage index test/reference standard (16)	Time interval (17)	Severity of disease (18)	Cross tabulation (19)	Adverse events (20)	Diagnostic accuracy and statistical uncertainty (21)	Indeterminate results or outliers (22)	Variability of diagnostic accuracy (23)	Estimates of test reproducibility (24)	Clinical applicability (25)
Contrast Enema										
Cho, 1990	All patients underwent index test 39% underwent high validity reference testing (surgery) 61% low validity reference testing (clinical follow-up)	Interval between BE/CT, *n*=13 1-3 days, *n*=4 4-7 days *n*=21 immediately after CT any treatment in between not mentioned	Complicated ACD, *n*=16 (60%) defined as presence of abscess	BE: Patients with diverticulitis: TP 20 FN 5 Patients without diverticulitis: TN 25 FP 0 Patients with diverticulitis 25/27 (93%) underwent BE CT: Patients with diverticulitis: TP 25 FN 2 Patients without diverticulitis: TN 29 FP 0 All patients with diverticulitis underwent CT All patients accounted for	None	BE: Sens: 0.80 Spec: 1.00 LR +: Infinity LR-: 0.2 NPV: 0.83 PPV: 1.00 CT: Sens: 0.93 Spec: 1.00 LR +: Infinity LR-: 0.07 NPV: 0.94 PPV: 1.00	None reported	Not reported	Not reported	Accuracy of clinical diagnosis 48% Adequate clinical applicability
Stefánsson, 1997	84/88 (95%) patients underwent CT and CE 2 only CT and 2 only CE second half of study period laparoscopy performed in subgroup of consecutive patients (subgroup inclusion criteria not mentioned) 30/46 (65%) 34% underwent high validity reference testing (surgery, i.e. laparoscopy) 66% low validity reference testing (clinical follow-up)	Interval between CT and CE 0-7 days (median 3 days) Interval between CT/CE and laparoscopy not mentioned	Complicated ACD, *n*=6 (12%) defined as presence of abscess	BE: Patients with diverticulitis: TP 43 FN 9 Patients without diverticulitis: TN 29 FP 7 Patients with diverticulitis 86/88 (98%) underwent BE CT: Patients with diverticulitis: TP 36 FN 16 Patients without diverticulitis: TN 36 FP 0 86/88 (98%) underwent BE All patients accounted for	Small bowel perforation, treated successfully with open surgery, uncomplicated abdominal wall hematoma with laparoscopy	BE: Sens: 0.83 Spec: 0.81 LR +: 4.25 LR-: 0.21 NPV: 0.76 PPV: 0.86 CT: Sens: 0.69 Spec: 1.00 LR +: Infinity LR-: 0.31 NPV: 0.69 PPV: 1.00	None reported	Not reported	Not reported	Laparoscopy nowadays not done to confirm or rule out diagnosis, not clear why used in this article, subgroups undergoing laparoscopy not clearly defined makes clinical applicability less reliable

Table S2: Quality assessment of included studies based on the STARD initiative checklist (continued II)

Study / year	Percentage index test/reference standard (16)	Time interval (17)	Severity of disease (18)	Cross tabulation (19)	Adverse events (20)	Diagnostic accuracy and statistical uncertainty (21)	Indeterminate results or outliers (22)	Variability of diagnostic accuracy (23)	Estimates of test reproducibility (24)	Clinical applicability (25)
Ultrasound										
Verbanck , 1989	19 % underwent high validity reference testing (surgery) 81%% low validity reference testing, combination of endoscopy (*n*=5) and/or CE (*n*=43) reference testing is only given for patients with final diagnosis ACD, it is unclear how reference testing is done in patients with an alternative diagnosis	Interval between admittance and US within 24 hours	Complicated ACD, *n*=8 (16%) defined as presence of abscess	Patients with diverticulitis: TP 44 FN 8 Patients without diverticulitis: TN 57 FP 14 All patients accounted for	None	Sens: 0.85 Spec: 0.80 LR +:4.29 LR-: 0.19 NPV: 0.88 PPV: 0.75	None reported	Not reported	Not reported	Adequate clinical applicability Reflects everyday practice US drainage was done in case of abscess Accuracy of clinical diagnosis 42%
Schwerk, 1992	*N*=24 (15%) underwent high validity reference testing (surgery) 85%% low validity reference testing, combination of endoscopy, radiographic measures and/or clinical follow-up Reference testing is clearly stated in the article en divided in patients with ACD, patients with a specific other abdominal condition and patients with nonspecific abdominal pain	Interval between admittance and US not mentioned	Complicated ACD, *n*=13 (25%) defined as presence of abscess	Patients with diverticulitis: TP 51 FN 1 Patients without diverticulitis: TN 76 FP 2 All patients accounted for	None	Sens: 0.98 Spec: 0.97 LR +: 38.25 LR-: 0.02 NPV: 0.99 PPV: 0.96	None reported	Not reported	Not reported	Reflects every day practice Double publication Accuracy of clinical diagnosis 40%
Zielke, 1997	All patients underwent index test and reference test High validity reference test: 43% (*n*=32, surgery) Low validity reference test: 57% (*n*=42)	Unknown or inadequately reported	Complicated ACD, *n*=11 (15%) defined as presence of abscess	Patients with diverticulitis: TP 62 FN 12 Patients without diverticulitis: TN 64 FP 5 All patients accounted for	None	Sens: 0.84 Spec: 0.93 LR +: 11.56 (7.76-17.12) LR-: 0.17 (0.15-0.21) NPV: 0.84 PPV: 0.93	None reported	Not reported	Not reported	Accuracy of clinical diagnosis 53% Adequate clinical applicability reflects daily practice

Table S2: Quality assessment of included studies based on the STARD initiative checklist (continued II)

Study / year	Percentage index test/reference standard (16)	Time interval (17)	Severity of disease (18)	Cross tabulation (19)	Adverse events (20)	Diagnostic accuracy and statistical uncertainty (21)	Indeterminate results or outliers (22)	Variability of diagnostic accuracy (23)	Estimates of test reproducibility (24)	Clinical applicability (25)
Hollerweger, 2000	All patients underwent index test and reference test High validity reference test: 22% (*n*=39 surgery in combination with histology reports) Low validity reference test: 78% consensus opinion based on clinical data, laboratory parameters and results of imaging procedures (*n*=57 CT, *n*=48 colonoscopy, n=27 contrast enema)	Unknown or inadequately reported	Complicated ACD, *n*=24 (24%) defined as presence of abscess, fistula or perforation	Patients with diverticulitis: TP 96 FN 6 Patients without diverticulitis: TN 71 FP 2 All patients accounted for	None	Sens: 0.94 Spec: 0.97 LR +: 34.35 LR-: 0.06 NPV: 0.98 PPV: 0.92	None reported	Not reported	Not reported	Adequate clinical applicability
US vs CT										
Pradel, 1997	All patients underwent index test and reference test High validity reference test: 55% (*n*=18, surgery) Low validity reference test: 45% (*n*=15)	Interval between CT and US as short as possible (less than 2 hours in most cases and never more than 24 hours)	Complicated ACD, *n*=9 (27%) defined as presence of abscess	US: Patients with diverticulitis: TP 28 FN 5 Patients without diverticulitis: TN 26 FP 5 All patients accounted for CT: Patients with diverticulitis: TP 30 FN 3 Patients without diverticulitis: TN 24 FP 7 All patients accounted for	None	US: Sens: 0.85 Spec: 0.84 LR +: 5.26 (3.15-7.88) LR-: 0.18 (0.18-0.27) NPV: 0.84 PPV: 0.85 CT: Sens: 0.91 Spec: 0.77 LR +: 4.03 (3.03-5.36) LR-: 0.12 (0.06-0.23) NPV: 0.84 PPV: 0.85	None reported	Not reported	Not reported	Accuracy of clinical diagnosis 52% Adequate clinical applicability

Table S2: Quality assessment of included studies based on the STARD initiative checklist (continued II)

Study / year	Percentage index test/reference standard (16)	Time interval (17)	Severity of disease (18)	Cross tabulation (19)	Adverse events (20)	Diagnostic accuracy and statistical uncertainty (21)	Indeterminate results or outliers (22)	Variability of diagnostic accuracy (23)	Estimates of test reproducibility (24)	Clinical applicability (25)
Farag Soliman, 2004	All patients underwent index test and reference test High validity reference test: 54% (*n*=34, surgery in combination with histopathology) Low validity reference test: 46% (*n*=29, clinical follow-up)	Interval between admittance and US <24 hours Between admittance and CT also <24 hours	Complicated ACD, *n*=20 (47%) defined as presence of abscess, perforation or fistel	US: Patients with diverticulitis: TP 43 FN 0 Patients without diverticulitis: TN 20 FP 0 All patients accounted for CT: Patients with diverticulitis: TP 42 FN 1 Patients without diverticulitis: TN 20 FP 0 All patients accounted for	None	US: Sens: 1.00 Spec: 1.00 LR +: infinity LR-: infinity NPV: 1.00 PPV: 1.00 CT: Sens: 0.98 Spec: 1.00 LR +: infinity LR-: 0.02 NPV: 0.95 PPV: 1.00	None reported	Not reported	Not reported	Adequate clinical applicability
CT										
Doringer, 1990	All patients underwent index test and reference test High validity reference test: 27% (*n*=9, surgery in combination with histopathology) Low validity reference test: 73% (*n*=24, clinical follow-up)	Unknown or inadequately reported	Complicated ACD, *n*=2 (10%) defined as presence of abscess	Patients with diverticulitis: TP 20 FN 1 Patients without diverticulitis: TN 9 FP 3 All patients accounted for	None	Sens: 0.95 Spec: 0.75 LR +: 3.81 LR-: 0.06 NPV: 0.90 PPV: 0.87	None reported	Not reported	Not reported	Study mainly done to identify specific CT findings indicative for diverticulitis Numbers small, relatively little patients with complicated diverticulitis Reasonable clinical applicability
Rao, 1998	All patients underwent index test and reference test High validity reference test: 28% (*n*=41, histopathology) Low validity reference test: 72%	Unknown or inadequately reported	Complicated ACD, *n*=13 (20%) defined as presence of abscess, fistula, free air or fluid	Patients with diverticulitis: TP 62 FN 2 Patients without diverticulitis: TN 86 FP 0 All patients accounted for	None	Sens: 0.97 Spec: 1.00 LR +: Infinity LR-: 0.03 NPV: 0.98 PPV: 1.00	None reported	Not reported	Not reported	Adequate clinical applicability

Table S2: Quality assessment of included studies based on the STARD initiative checklist (continued II)

Study / year	Percentage index test/reference standard (16)	Time interval (17)	Severity of disease (18)	Cross tabulation (19)	Adverse events (20)	Diagnostic accuracy and statistical uncertainty (21)	Indeterminate results or outliers (22)	Variability of diagnostic accuracy (23)	Estimates of test reproducibility (24)	Clinical applicability (25)
Werner, 2003	All patients underwent index test and reference test High validity reference test: 41% (*n*=49, histopathology) Low validity reference test: 72%	CT within 24 hours after hospital admittance	Complicated ACD, *n*=11 (16%) defined as presence of abscess or contained or free perforation	Patients with diverticulitis: TP 65 FN 2 Patients without diverticulitis: TN 52 FP 1 All patients accounted for	None	Sens: 0.97 Spec: 0.98 LR +: 51.4 LR-: 0.03 NPV: 0.97 PPV: 0.98	None reported	Not reported	Not reported	Adequate clinical applicability
Tack, 2005	All patients underwent index test and reference test High validity reference test: 67% (*n*=74, histopathology) Low validity reference test: 33% (*n*=36, clinical follow-up)	Time between index test and colonoscopy (in 50% of the cases) was unknown	Complicated ACD, *n*=14 (36%) defined as high grade diverticulitis abscess formation, gaseous collection and or fistula	Patients with diverticulitis: TP 36 FN 3 Patients without diverticulitis: TN 70 FP 1 All patients accounted for	None	Sens: 0.92 Spec: 0.99 LR +: 65.5 LR-: 0.08 NPV: 0.96 PPV: 0.98	None reported	Not reported	Not reported	Comparison between two CT regimes shows that sens/spec were similar regardless of dose and CT has good potential to depict alternative disease Adequate clinical applicability
MRI										
Heverhagen, 2008	All patients underwent index test and reference test High validity reference test: 29% (*n*=16, histopathology) Low validity reference test: 71% (*n*=39, clinical follow-up including CT in *n*=31 patients, 57%)	Not mentioned	Not mentioned	Assessor 1: Patients with diverticulitis: TP 45 FN 2 Patients without diverticulitis: TN 7 FP 1 All patients accounted for Assessor 2: Patients with diverticulitis: TP 46 FN 3 Patients without diverticulitis: TN 7 FP 1 All patients accounted for	None	Sens: 0.94-0.96 Spec: 0.88 LR +: 7.55-7.66 LR-: 0.05-0.07 NPV: 0.70-0.77 PPV: 0.98	None reported	Not reported	Not reported	Adequate clinical applicability

Table S2: Quality assessment of included studies based on the STARD initiative checklist (continued II)

Study / year	Percentage index test/reference standard (16)	Time interval (17)	Severity of disease (18)	Cross tabulation (19)	Adverse events (20)	Diagnostic accuracy and statistical uncertainty (21)	Indeterminate results or outliers (22)	Variability of diagnostic accuracy (23)	Estimates of test reproducibility (24)	Clinical applicability (25)
Clinical diagnosis										
Laurell , 2006	All patients underwent index test but is unclear how many patients had the complete reference test meaning not only diagnostic criteria for diverticulitis but also finding of diverticula at X-ray or endoscopic examination CT was used in a minority of uncomplicated cases (4%) and was more common in complicated cases (with perforation 36%)	Unknown	Complicated ACD, *n*=11 (8%) defined as perforated diverticulitis	TP/TN not separately mentioned but could be calculated from table. Patients with diverticulitis: TP 93 FN 52 Patients without diverticulitis: TN 1049 FP 46 All patients accounted for	None	Sens: 0.64 Spec: 0.97 LR +: 15.27 LR-: 0.37 NPV: 0.95 PPV 0.67	After scrutinizing the Emergency Department register another 16 patients were found who should have been in the data base register	A validation of 10% of the patients in the database was performed	Not reported	Accuracy of clinical diagnosis is difficult. Specificity is fairly high in preliminary diagnosis and discharge diagnosis but the low sensitivity remains the problem
Toorenvliet , 2008	Of the 60 patients with suspected colonic diverticulosis 95% underwent additional imaging *n*=57 proved to have ACD *n*=8 surgery (14%) confirmation with barium enema and colonoscopy in 41 patients (72%) High validity reference test Reference testing for the patients not having ACD not mentioned	Unknown	Complicated ACD, *n*=3 (stenosis), *n*=3 colovesical fistula, *n*=6 pericolic abscess 72% uncomplicated diverticulitis	Patients with diverticulitis: TP 30 FN 14 Patients without diverticulitis: TN 728 FP 16 All patients accounted for	None	Sens: 0.68 Spec: 0.98 LR +: 32 LR-: 0.33 NPV: 0.98 PPV: 0.65	None reported	Not reported	Not reported	Clinical diagnosis had a high specificity but a low sensitivity

STARD initiative checklist
(16) The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).
(17) Time-interval between the index tests and the reference standard, and any treatment administered in between.
(18) Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.
(19) A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.
(20) Any adverse events from performing the index tests or the reference standard.
(21) Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).
(22) How indeterminate results, missing data and outliers of the index tests were handled.
(23) Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.
(24) Estimates of test reproducibility, if done.
(25) Discuss the clinical applicability of the study findings.

Chapter 5

The disease course of right- and left-sided diverticulitis in a Western population

Johannes Wegdam

Caroline Andeweg

Timme van Vuuren

Tammo de Vries Reilingh

Hester van der Zaag-Loonen

Harry van Goor

Submitted

Abstract

Background
Right-sided colonic diverticulitis is a rare disorder in Western patients and is considered to behave more aggressively than left-sided diverticulitis.

Objective
This study evaluates the differences in the disease course between right- and left-sided diverticulitis in a Western population.

Patients
Adult patients hospitalized between 2004 and 2008 with an episode of acute diverticulitis confirmed by imaging were divided in two groups of patients with a right- or a left-sided diverticulitis.

Main outcome measures
Differences in incidence, patient characteristics, clinical presentation and disease course between the two groups.

Results
The hospital coding system yielded 425 patients with a diverticulitis discharge code. A total of 183 patients was admitted with confirmed acute diverticulitis by imaging. The incidence of right-sided diverticulitis was 8%. Patients with right-sided diverticulitis were predominantly female, 86% compared to 47% in left sided diverticulitis (p=0.05). Median CRP at presentation was lower in right sided diverticulitis, 30 compared to 71mg/l (p=0.001). No other significant differences in clinical presentation and disease course were found between right and left-sided diverticulitis.

Conclusions
Acute right-sided diverticulitis in Western patients has a low incidence, affects predominantly females and presents with a lower CRP than patients with left-sided diverticulitis. Clinical presentation and disease course are comparable.

Introduction

The type and location of diverticula in the colon differ between populations living in the Eastern and Western hemisphere resulting in different patterns of diverticulitis.[1-5] Right-sided colonic diverticulitis (RCD) is common in Asia, but is rare in Europe and the USA. RCD in Asians originates mainly from congenital, solitary true diverticula in the cecum.[5] It is not clear if RCD in Western patients also originates from true diverticula or is a consequence of acquired pseudo-diverticula with a left to right sequence.[6] The difference in etiology has led to the assumption that RCD and left-sided diverticulitis (LCD) in Western patients have different disease courses.

The clinical picture of RCD resembles that of acute appendicitis. In the era before widespread use of imaging, an inflamed cecum was encountered as unexpected finding during intended appendectomy. Emergency resection of the inflamed colonic segment usually was performed to eradicate the origin of the inflammation, possibly a malignancy.[1-3, 6-9] Aggressive treatment of RCD by removing all apparent disease at the time of initial presentation was also justified because of studies reporting severe complications after conservative treatment of RCD.[1, 6, 10] The high operative rate of RCD precluded the knowledge on the natural disease course of RCD in Western patients and the effect of conservative treatment, and led to the opinion that RCD is a more aggressive disease than LCD and needs a different, less conservative approach.[9, 11-14]

The routine use of radiological imaging in the diagnostic work-up of patients with acute abdominal pain caused a pivotal shift from a surgical diagnosis for RCD and a clinical diagnosis for LCD to both radiological diagnoses. This change has contributed to a better evaluation of the natural course of both diseases and their treatment managements. Current guidelines recommend a more conservative approach in patients with LCD.[15] Asian groups advocate an identical approach in the RCD patients, but treatment guidelines for Western patients with RCD are lacking.[11-14]

We hypothesize that the disease course and treatment of RCD is similar to LCD in Western patients, when RCD is established by imaging instead of by surgery. To this purpose we retrospectively analyzed a consecutive series of patients who were admitted to the hospital with right or left-sided diverticulitis with an adequate radiological diagnostic work up.

Material and methods

Patients

This retrospective study was performed in a non-teaching hospital in the Netherlands with an adherence of 175,000 persons and encompasses a 5-year period, from January 2004 to

December 2008. We searched the electronic hospital information system for the Diagnosis Treatment Combination (DTC) code for diverticular disease/diverticulitis (code 327) to identify all consecutive emergency patients admitted with left or right-sided diverticulitis, who were potentially eligible for inclusion in the study.

Inclusion criteria

All consecutive patients admitted for conservative or operative management of clinically and radiologically confirmed acute LCD or RCD were included. Diverticulitis was considered to be clinically suspect if the patient presented a history of pain at the left and/or right lower abdomen combined with at least one of the following elevated inflammatory parameters: temperature (T) >37.5° Celsius, erythrocyte sedimentation rate (ESR) >10mm/hr, or white blood cell count (WBC) >10.000/m^3 or C-reactive protein (CRP) >5mg/l. Radiological diagnosis of diverticulitis was established if at least one imaging modality, ultrasonography (US) or computed tomography (CT), performed within one week after admission, demonstrated signs of acute LCD or RCD: colonic wall thickness greater than 4mm, pericolic fat displaying straining and/or signs of complicated diverticulitis like pericolic abscess, pelvic abscess, extraluminar fluid, air or contrast.[16] Acute diverticulitis located in the cecum, ascending colon or proximal transverse colon was classified as RCD. Diverticulitis in the rest of the colon was defined as LCD.

The Hinchey-Wasvary classification (stage 0-IV) was used to stage acute diverticulitis. (*Table 1*) Hinchey-Wasvary stages 0 and I were considered mild and stages II-IV severe diverticulitis.[16]

Data extraction

The following data were extracted from the electronic and hardcopy medical records: Patient characteristics: age, gender, previous appendectomy, previous episode(s) of diverticulitis; Clinical presentation: location of abdominal pain, presence of vomiting, body temperature in degrees Celsius; Laboratory findings: (erytrocyte sedimentation rate (ESR) in mm/h, white blood cell count (WBC) in 103/l and C-reactive protein (CRP) in mg/l); Radiological findings: type of imaging modality (US and/or CT) for the final diagnosis. Clinical course: conservative or operative management, early operative management (within 30 days after initial hospital admission) and length of hospital stay (days). In case of RCD, follow-up investigations, i.e., colonoscopy (CS) and colonic enema (CE) were documented and patients were interviewed by telephone regarding the number of recurrences and surgery for RCD. The duration of follow up was defined by the number of years between the first admission for RCD and last months of data accrual (September 2013).

Statistical analysis

The t-test for two independent groups was used to test differences between patients with RCD and LCD in case of normally distributed continuous variables; for not-normally distributed data the Mann-Whitney U test was used. The Chi-square test was used in case

of nominal data, and the Fisher exact test in case of small groups of patients (*n* <10). A value of *p* less than 0.05 was considered statistically significant. SPSS software (PASW statistics 20.0) was used to analyze data.

Results

The hospital information system revealed 425 patients with the DTC-code diverticular disease/diverticulitis during the 5-year study period of whom 183 were eligible for analysis (*Figure 1*).

A total of fourteen patients (8%) were diagnosed with RCD. *Table 2* summarizes the annual incidence of RCD compared to LCD.

Table 3 summarizes the patient characteristics and clinical outcome of patients with acute LCD and RCD. In the RCD group females were significantly overrepresented (*p*=0.05) and CRP at admission was significantly lower (*p*=0.001). No significant differences were found in other patient characteristics, clinical presentation or disease course data between patients with RCD and with LCD. More specifically the percentage of severe diverticulitis cases and of operative treatment was comparable.

Table 4 describes patient characteristics and clinical outcome of all patients with acute RCD in detail. Two out of 14 RCD patients underwent immediate surgery after initial radiological imaging. Both patients had inconclusive radiological findings of an atypical appendicitis or cecal diverticulitis. A gridiron incision was performed in both patients and an inflamed cecum with a normal appendix was seen. Uncertainty concerning the diagnosis led to ileocecal resection in both patients. Both recovered uneventful. Histopathological examination demonstrated a non-inflamed appendix and a solitary inflamed diverticulum in the cecum in both cases. The 12 remaining RCD patients were successfully managed by conservative means with a median hospital stay of six days. One patient had a prolonged hospital stay for non-RCD related reasons. All RCD patients had a follow up with a median time of seven (range 5-10) years. Follow-up colonoscopy was not performed in one patient due to significant co-morbidities and refused by another patient. Only one patient, a 31-year old female, experienced a second episode of RCD (recurrence rate 7%), which was again successfully treated without operation. None of the RCD patients had late elective or acute surgery for RCD during the follow-up period. Combining the radiological findings with the postoperative pathology reports or follow-up colonoscopy reports, it was concluded that ten patients had a solitary diverticulum and four patients had multiple diverticula present in the cecum and ascending colon.

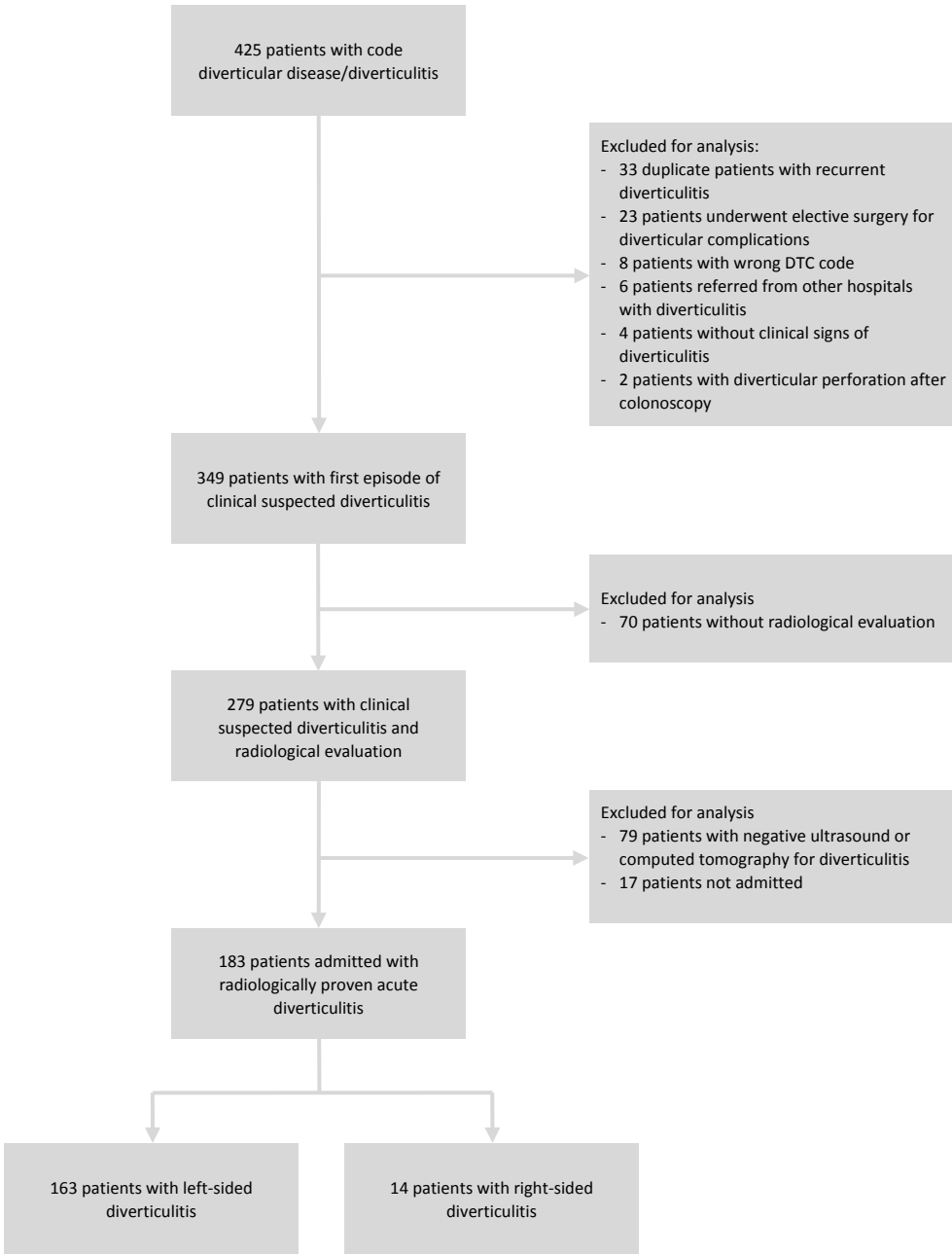


Figure 1: Flow-chart for patient selection with right-sided or left-sided diverticulitis based on diagnosis treatment combination-code (DTC-code) diverticular disease/diverticulitis in 5-year study period

Table 1: Hinchey-Wasvary classification for acute diverticulitis

0	Direct visualization of the diverticulum with symptoms
Ia	Confined pericolic inflammation (phlegmon)
Ib	Confined pericolic abscess
II	Distant intra-abdominal or retroperitoneal abscess
III	Generalized purulent peritonitis
IV	Fecal peritonitis

Table 2: Annual incidence of patients with confirmed right- and left-sided diverticulitis

	2004	**2005**	**2006**	**2007**	**2008**	**Total**
RCD patients	2	6	1	2	3	14
LCD patients	37	31	35	39	27	169
Total	39	37	36	41	30	183
Incidence of RCD	5%	16%	3%	5%	10%	8%

LCD: left-sided colonic diverticulitis; RCD: right-sided colonic diverticulitis

Table 3: Patient characteristics and clinical outcome of patients with confirmed acute right- and left-sided diverticulitis

	RCD (14)	**LCD (169)**	***p* value**
Patient characteristics			
mean age (years)	53 (SD 15,3)	56 (SD 12,8)	0,84
gender (M/F)	2/12 (14%)	90/79 (53%)	0,05
appendicitis in medical history	4 (29%)	23 (14%)	0,13
diverticulitis in medical history	2 (14%)	41 (24%)	0,53
Clinical presentation			
pain left lower abdomen	0	159 (94%)	
pain right lower abdomen	14 (100%)	51 (30%)	
pain left and right lower abdomen	0	41 (24%)	
vomitus	2 (14%)	24 (14%)	0,73
mean body temperature	37.0 (SD 0,6)	37.4 (SD 0.8)	0,09
median CRP	30 (5-228)	71 (1-413)	<0,01
median WBC	13.2 (6.5-27.7)	13.2 (1.5-27.4)	0,79
median ESR	32 (2-78)	33 (0-149)	0,54
US performed	14 (100%)	162 (96%)	0,44
CT performed	6 (43%)	46 (27%)	0,23
mild diverticulitis	14 (100%)	154 (91%)	0,61
Clinical course			
median days of hospital stay	5.5 (3-8)	6.0 (1-49)	0,46
operative treatment <30 days	2 (14%)	18 (11%)	0,65

RCD: right-sided colonic diverticulitis; LCD: left-sided colonic diverticulitis; M: male; F: female; CRP: C-reactive protein (mg/l); WBC: white blood cell count ($x10^3$/l); ESR: erythrocyte sedimentation rate (mm/h); US: Ultrasound; CT: Computed Tomography

Table 4: Patient characteristics and clinical outcome of patients with acute right-sided diverticulitis

Case No, age/sex	Clinical diagnosis	DoS (days)	T	ESR	WBC	CRP	Modality	Radiological diagnosis	HW	Treatment	HS (days)	FU (years)	FU exam
1, 65/F	appendicitis	3	37.2	34	11,9	10	US	RCD/appendicitis	Ia	i.v. antibiotics	6	10	CE
2, 61/M	diverticulitis	1	36.9	2	17,6	21	US	RCD	Ia	i.v. antibiotics	5	8	CE+CS
3, 62/F	cholecystitis	1	35.4	5	27.7	10	US	RCD/Tumor/Crohn	Ia	i.v. antibiotics	5	8	CE
4, 73/F	diverticulitis	21	37.2	59	8.6	5	US	RCD/Tumor	Ia	i.v. antibiotics	8	6	CE+CS
5, 67/F	RCD/appendicitis	2		72	12.6	43	US	RCD	Ia	i.v. antibiotics	6	6	CS
6, 31/F	appendicitis	5	37.5	36	15.2	40	US	RCD	Ia	i.v. antibiotics	5	6	CS
7, 39/F	appendicitis	1	37.2	78	13.8	161	US	RCD	Ia	supportive	3	5	CE+CS
8, 54/F	pyelonephritis	14	37.1	42	8.3	60	US+CT	RCD/Tumor	Ia	i.v. antibiotics	8	6	CS
9, 61/F	appendicitis	2	36.3	26	9.1	8	US+CT	RCD/Tumor	Ia	i.v. antibiotics	5	8	CS
10, 41/F	appendicitis/RCD	3	36.7	2	16.2	11	US+CT	appendicitis/RCD	Ia	ileocecal resection	3	9	none
11, 51/F	appendicitis	2	37.4	41	16.5	43	US+CT	RCD/appendagitis	Ia	i.v. antibiotics	7	8	none
12, 44/F	gastroenteritis	1	37.7	6	20.0	50	US+CT	RCD	Ia	i.v. antibiotics	7	8	CE
13, 78/M	appendicitis	2	37.5		6.5	39	US+CT	RCD	Ia	i.v. antibiotics	6	7	none
14, 44/F	appendicitis	2		8	9.9	16	US	appendicitis/RCD	Ia	ileocecal resection	4	9	none

No: number; DoS: duration of symptoms; T: body temperature (°Celsius); ESR: erythrocyte sedimentation rate (mm/h); WBC: white blood cell count ($x10^3$/l); CRP: C-reactive protein (mg/l); HW: Hinchey-Wasvary classification; HS: hospital stay; FU: Follow-up; FUex: Follow-up exams; M: male; F: female; Age (years); US: Ultrasound; CT: Computed tomography; RCD: right-sided diverticulitis; CE: colonic enema; CS: colonoscopy

Discussion

The primary aim of this study was to evaluate the differences in the disease course of right- and left-sided diverticulitis in Western patients. Results of this study demonstrated that RCD is about twelve times less common than LCD in a cohort of Western patients and has a predominance for females. The disease course and treatment approach of RCD resemble that of LCD.

The clinical presentation of LCD or RCD is known to mimic that of other diseases. Based on clinical findings alone the diagnosis of diverticulitis is often inaccurate and therefore imaging is recommended in the diagnostic process of diverticulitis.[17] Major strength of this study is the use of radiologically proven diverticulitis. This excludes the erroneous inclusion of patients with an assumed but later unconfirmed diagnosis of diverticulitis.

Interpretation of the results is limited by the retrospective nature of this study, the single center design and the relatively small number of RCD patients compared to LCD patients. The use of a diagnostic code to identify eligible diverticulitis patients may have resulted in a relative underestimation of the true incidence of RCD. RCD may have been unrecognized because not every patient presenting with acute indeterminate right lower abdominal pain has routine radiological evaluation. In general, the interpretation of many study results on diverticulitis is hampered by the lack of a classifying diagnosis based on radiological imaging. Comparing RCD with LCD is even more difficult because most studies on RCD in Caucasians lack pre-operative radiological evaluation and are based on intra-operative findings. The 8% prevalence of RCD is in accordance with that reported in literature.[7, 10, 18] This percentage varies between 60-90% in Asians with acute diverticulitis.[4, 19] Our study shows a predominant prevalence of RCD in elderly females in contrast to young males in Asian studies.[20] RCD in elderly female patients suggests an acquired origin of diverticula at the right side similar to that at the left side. However, in more than 70% of our patients RCD originated from solitary diverticula, indicative of true diverticula. Whether a right-sided diverticulum is a true congenital or an acquired pseudo-diverticulum, this study demonstrates that the clinical outcome is not different from LCD in Caucasian patients.

Arguments exist to believe that RCD had a milder clinical course than LCD in our patients based on a lower level of the inflammatory parameter CRP and the lower rate of severe diverticulitis at presentation. Perforated RCD with distant abdominal abscesses or fecal peritonitis has rarely been described in Western patients. In addition, recurrence rate of RCD (7% in 7 years in our study) seems lower than that of LCD (up to 20% in 10 years).[14-16, 19, 21-25]

Successful results of non-operative management of uncomplicated RCD in both Western and Asian patients have been published before.[4, 10-12, 14, 26-30] All but one of the RCD

patients received antibiotics as part of the conservative treatment, which is questionable for patients with mild RCD similar to patients with LCD.[31, 32] Oudenhoven and Lee demonstrated excellent results from non-antibiotic treatment for RCD.[4, 26] No need for antibiotics and successful conservative treatment in the majority of patients supports the theory that RCD in Western patients is a self-limiting disease. The mild clinical presentation of RCD may also explain the relative low incidence of RCD in the Western world whereby most patients are not referred to a hospital and remain undiagnosed.

Conclusion

Radiologically proven RCD in Western patients has a low incidence, develops predominantly in females, is a self-limiting disease in most cases and seems to have a milder disease course compared with LCD.

The concept that RCD in Western patients is a more aggressive disease than LCD is merely a reflection of the unfamiliarity with this disease in the Western world, and inadequate diagnostic workup and decision making in the operating room.

An adult Caucasian patient over 50 years with pain in the lower right abdomen suspected of an acute inflammatory process benefits from radiological imaging to avoid unnecessary surgery for RCD. Imaging allows clinicians to determine the optimal management according to the severity of the diverticulitis.[27] Taking into account the similar mild or even milder disease course found in this study current guidelines for the treatment of LCD also can apply for the treatment of RCD.[33]

Reference list

1 Sardi A, Gokli A, Singer JA. Diverticular disease of the cecum and ascending colon. A review of 881 cases. The American surgeon 1987;53:41-5.

2 Katz DS, Lane MJ, Ross BA, Gold BM, Jeffrey RB, Jr., Mindelzun RE. Diverticulitis of the right colon revisited. AJR American journal of roentgenology 1998;171:151-6.

3 Hildebrand P, Kropp M, Stellmacher F, Roblick UJ, Bruch HP, Schwandner O. Surgery for right-sided colonic diverticulitis: results of a 10-year-observation period. Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie 2007;392:143-7.

4 Lee IK. Right colonic diverticulitis. Journal of the Korean Society of Coloproctology 2010;26:241-5

5 Miura S, Kodaira S, Shatari T, Nishioka M, Hosoda Y, Hisa TK. Recent trends in diverticulosis of the right colon in Japan: retrospective review in a regional hospital. Diseases of the colon and rectum 2000;43:1383-9.

6 Lane JS, Sarkar R, Schmit PJ, Chandler CF, Thompson JE, Jr. Surgical approach to cecal diverticulitis. Journal of the American College of Surgeons 1999;188:629-34; discussion 34-5.

7 Violi V, Roncoroni L, Boselli AS, Trivelli M, Peracchia A. Diverticulitis of the caecum and ascending colon: an unavoidable diagnostic pitfall? International surgery 2000;85:39-47.

8 Fang JF, Chen RJ, Lin BC, Hsu YB, Kao JL, Chen MF. Aggressive resection is indicated for cecal diverticulitis. American journal of surgery 2003;185:135-40.

9 Ngoi SS, Chia J, Goh MY, Sim E, Rauff A. Surgical management of right colon diverticulitis. Diseases of the colon and rectum 1992;35:799-802.

10 Reisman Y, Ziv Y, Kravrovitc D, Negri M, Wolloch Y, Halevy A. Diverticulitis: the effect of age and location on the course of disease. International journal of colorectal disease 1999;14:250-4.

11 Park HC, Chang MY, Lee BH. Nonoperative management of right colonic diverticulitis using radiologic evaluation. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland 2010;12:105-8.

12 Kim MR, Kye BH, Kim HJ, Cho HM, Oh ST, Kim JG. Treatment of right colonic diverticulitis: the role of nonoperative treatment. Journal of the Korean Society of Coloproctology 2010;26:402-6.

13 Yang HR, Huang HH, Wang YC, Hsieh CH, Chung PK, Jeng LB, Chen RJ. Management of right colon diverticulitis: a 10-year experience. World journal of surgery 2006;30:1929-34.

14 Moon HJ, Park JK, Lee JI, Lee JH, Shin HJ, Kim WS, Kim MS, Jeong JH. Conservative treatment for patients with acute right colonic diverticulitis. The American surgeon 2007;73:1237-41.

15 McDermott FD, Collins D, Heeney A, Winter DC. Minimally invasive and surgical management strategies tailored to the severity of acute diverticulitis. The British journal of surgery 2014;101:e90-9.

16 Ambrosetti P, Becker C, Terrier F. Colonic diverticulitis: impact of imaging on surgical management -- a prospective study of 542 patients. European radiology 2002;12:1145-9.

17 Rafferty J, Shellito P, Hyman NH, Buie WD. Practice parameters for sigmoid diverticulitis. Diseases of the colon and rectum 2006;49:939-44.

18 Fluckiger R, Styger S, Huber A. [Diverticulitis of the cecum and ascending colon]. Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen 1998;69:174-9.
19 Kim SH, Byun CG, Cha JW, Choi SH, Kho YT, Seo DY. Comparative study of the clinical features and treatment for right and left colonic diverticulitis. Journal of the Korean Society of Coloproctology 2010;26:407-12.
20 Sugihara K, Muto T, Morioka Y, Asano A, Yamamoto T. Diverticular disease of the colon in Japan. A review of 615 cases. Diseases of the colon and rectum 1984;27:531-7.
21 Tan KK, Liu JZ, Shen SF, Sim R. Emergency surgery in colonic diverticulitis in an Asian population. International journal of colorectal disease 2011;26:1045-50.
22 Law WL, Lo CY, Chu KW. Emergency surgery for colonic diverticulitis: differences between right-sided and left-sided lesions. International journal of colorectal disease 2001;16:280-4.
23 Laméris W, van Randen A, Bipat S, Bossuyt PM, Boermeester MA, Stoker J. Graded compression ultrasonography and computed tomography in acute colonic diverticulitis: meta-analysis of test accuracy. European radiology 2008;18:2498-511.
24 Giuffrida MC, Gelarda E, Mezzatesta P, Macaluso A, Siragusa G. [Diverticula of the right colon. The diagnosis and treatment of complications]. Minerva chirurgica 1997;52:1503-12.
25. Jacobs DO. Clinical practice. Diverticulitis. The New England journal of medicine 2007;357:2057-
26 Oudenhoven LF, Koumans RK, Puylaert JB. Right colonic diverticulitis: US and CT findings--new insights about frequency and natural history. Radiology 1998;208:611-8.
27 Park SJ, Choi SI, Lee SH, Lee KY. Image-guided conservative management of right colonic diverticulitis. World journal of gastroenterology : WJG 2009;15:5838-42.
28 Komuta K, Yamanaka S, Okada K, Kamohara Y, Ueda T, Makimoto N, Shiogama T, Furui J, Kanematsu T. Toward therapeutic guidelines for patients with acute right colonic diverticulitis. American journal of surgery 2004;187:233-7.
29 Park HC, Kim BS, Lee BH. Management of right colonic uncomplicated diverticulitis: outpatient versus inpatient management. World journal of surgery 2011;35:1118-22.
30 Park HC, Lee BH. Suspected uncomplicated cecal diverticulitis diagnosed by imaging: initial antibiotics vs laparoscopic treatment. World journal of gastroenterology 2010;16:4854-7.
31 Hjern F, Josephson T, Altman D, Holmström B, Mellgren A, Pollack J, Johansson C. Conservative treatment of acute colonic diverticulitis: are antibiotics always mandatory? Scandinavian journal of gastroenterology 2007;42(1):41-7.
32 Chabok A, Påhlman L, Hjern F, Haapaniemi S, Smedh K, AVOD Study Group. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. British journal of surgery 2012;99(4):532-9.
33 Andeweg CS, Mulder IM, Felt-Bersma RJ, Verbon A, van der Wilt GJ, van Goor H, Lange JF, Stoker J, Boermeester MA, Bleichrodt RP. Guidelines of diagnostics and treatment of acute left-sided colonic diverticulitis. Digestive Surgery 2013;30(4-6):278-92.

Chapter 6

Recurrent colonic diverticulitis: a Markov model to guide treatment

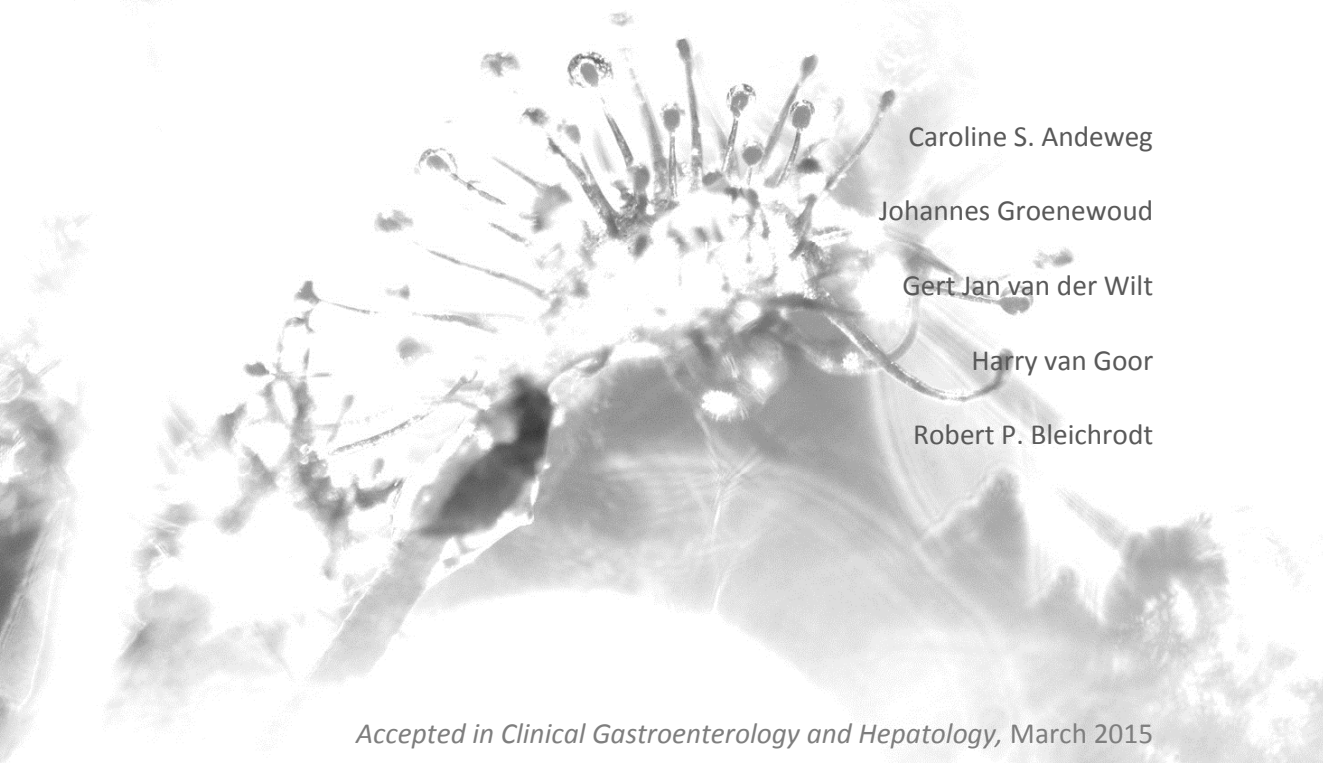
Caroline S. Andeweg

Johannes Groenewoud

Gert Jan van der Wilt

Harry van Goor

Robert P. Bleichrodt



Accepted in Clinical Gastroenterology and Hepatology, March 2015

Abstract

Background

Although colonic diverticulitis is a common disorder, the optimal treatment strategy for patients with recurrent episodes of diverticulitis remains unclear. We aimed to determine whether colonic resection, conservative or medical treatment, would be preferred treatment in terms of quality-adjusted life years (QALYs).

Method

A Markov model simulating patients with two episodes of non-surgically treated diverticulitis was used to simulate all relevant outcomes of each treatment strategy. A one-year cycle length with 10-year follow-up was used to allow for chance of recurrent diverticulitis. Primary outcome was QALYs gained from each strategy. Factors considered were morbidity, mortality, chance of colostomy formation, risk of recurrence and persisting abdominal pain. The probabilities of clinical events were determined using the best available data from the literature.

Results

The strategy in which colonic resection was performed after two episodes of diverticulitis was associated with the lowest quality-adjusted survival of 8.66 QALY, the highest chance of stoma formation (1.1%) but the lowest chance of a mild (3.5%) or severe (1.1%) recurrence. The strategies of colonic resection, conservative or medical treatment after the third episode of diverticulitis were comparable in terms of quality–adjusted survival, with 8.78, 8.76 and 8.74 QALYs, respectively. Probabilistic sensitivity analysis did not change these results. Persistent abdominal complaints were lowest in the medical treatment strategy.

Conclusion

Elective surgery after two episodes of diverticulitis should be questioned in terms of QALYs. After the third episode of diverticulitis surgical, conservative or medical treatment provide similar QALYs but rates of abdominal symptoms are lower in the medical treatment strategy. This Markov decision model has limitations when the individual patient and physician face a complex decision weighing early and long-term risks and benefits of elective surgery or conservative management.

Keywords

Diverticulitis; Quality of Life; recurrent disease; treatment options

Introduction

The main indication for elective colonic resection in patients with recurrent colonic diverticulitis is to prevent an emergency operation. Studies also suggest that elective resection reduces the burden of recurrent disease, lowers persistent abdominal complaints and treats symptomatic uncomplicated diverticular disease (SUDD).[1, 2] SUDD is a chronic illness characterized by persistent abdominal pain in between the overt flares of diverticulitis.[3]

To properly advise the individual patient with recurrent episodes of diverticulitis, it seems crucial to differentiate between patients who are likely to benefit from prophylactic resection to prevent complicated disease, and those who will have a benign course. The decision to recommend surgery seems affected by the age and medical condition of the patient, frequency and severity of the attack(s), and whether there are persistent symptoms after the acute episode.[4] Despite these new insights, evidence supporting the withheld of elective colectomy is still limited.[5]

Similarities between diverticulitis and inflammatory bowel disease have been demonstrated and potential beneficial results with medical therapy are being reported in small series.[6, 7] Results of medical treatment options have not been incorporated in recent guidelines, but might play a role in the decision whether or not to operate.

To determine the best strategy for patients with recurrent episodes of diverticulitis we designed a state-transition Markov model in which surgical and conservative treatment strategies in patients with recurrent episodes of diverticulitis were compared, with quality of life (QoL) as primary outcome measure. Quality of life was used because it encompasses best the different outcomes reported for treatment modalities of recurrent diverticulitis.

Material and methods

We constructed a Markov-based decision model to simulate the course of events for patients after two episodes of non-surgically treated acute colonic diverticulitis (ACD). TreeAge Pro 2009, release 1.0.2 was used to construct and analyze the Markov model.

Markov model

A simplified version of the Markov model is given in *Figure 1*. The model was designed from a patient perspective, using quality-adjusted life years (QALYs) as the overall outcome measure. The Markov model used a cycle time of one year and we ran the model for ten years to allow time for a diverticulitis recurrence. The base-case patient was a 58-year-old patient after two episodes of diverticulitis. The age-specific mortality rates for the

general population were taken from the Dutch mortality registry, which are comparable to other Western countries. We chose not to include patients of different age groups in the model to avoid major complexity and because high quality data to properly assign age related risks are lacking in literature.

Model strategies

After recovery from the second episode of diverticulitis patients undergo either colonic resection or a watch and wait 'treatment'. If colonic resection is performed (strategy 1), patients risk the chance of colostomy formation, major morbidity and mortality with the benefit of reducing the risk of recurrence with its accompanying chance of complicated disease, morbidity and mortality. Elective resection might also reduce persistent abdominal pain and IBS-like symptoms associated with recurrent episodes of diverticulitis. In case of a watch and wait policy, patients might completely recover and never experience a recurrent episode of ACD again. In case of recurrent disease there are four possibilities. The recurrence can be complicated necessitating emergency surgery with its own chance of colostomy formation, morbidity and mortality. In case of a mild recurrence, patients can either undergo colonic resection (strategy 2) or medical treatment can be initiated. Medical treatment can consist of conservative treatment with antibiotics for flares of diverticulitis only (strategy 3) or treatment with intermittent suppressive medical therapy (strategy 4). Both groups can re-enter the model again with the chance of having a next recurrent episode of diverticulitis. Patients with a Hartmann's procedure were considered candidates for a stoma reversal operation in the same model. Diverting ileostomy or colostomy after primary anastomosis and treatment with percutaneous drainage of abscesses were not considered in the model to avoid major complexity. During the simulation there were five possible health states in which patients could be: well with or without a colostomy, persisting abdominal pain with or without a colostomy, or dead.

Probabilities of clinical events

A Pubmed, Medline and Embase database search was conducted of articles published from January 1970 till June 2014 relevant to the subject of diverticulitis and natural history of the disease, conservative and/or operative treatment and/or reporting on chronic abdominal pain or abdominal symptoms (full search strategy available as supplemental material). A weighted mean was obtained for each variable and used as the baseline estimate, taking into account the number of patients that contributed to each outcome by each data source. Data extracted from the literature was used to obtain ranges for sensitivity analysis. (*Table 1*)

Recurrent ACD and medical treatment

The chance of recurrent diverticulitis was estimated at approximately 25% (range 9-29%) in a ten-year cycle length.[8-11] Each episode of diverticulitis predicts a higher risk of recurrence up to four recurrences.[8] The chance of having a recurrence that required emergency surgical intervention was estimated at 5.5%.[9, 11-14] Conservative measures in

case of recurrent episodes of diverticulitis are dietary changes, fiber supplementation and the use of antibiotic treatment for flares of diverticulitis only.[15] Medical treatment in the Markov model consisted of a non-absorbable antibiotic (rifaximin) combined with 5-aminosalicylic acid (mesalazine), which has been shown to reduce the severity of abdominal symptoms.[6, 16, 17] The role of medical treatment in preventing diverticulitis recurrence remains under debate, and a potential benefit in a decrement in recurrences was therefore not incorporated in the model.[6, 17, 18] Morbidity of medical treatment is defined as patients with persistent abdominal symptoms[14, 15, 19] and differs from surgical morbidity in the model. Calculated morbidity in the medical treatment strategy in the Markov model is corrected for by using the different utilities assigned to symptomatic and asymptomatic patients after recurrent episodes of ACD.

Elective surgery

Weighted averages of morbidity, mortality and chance of stoma formation after elective surgery are given in *Table 1*.[20-22] Both open- and laparoscopic surgical techniques were considered standard of care, having no difference in long-term outcomes.[21, 22] Surgical morbidity was defined as all major complications within 30 days that required radiological or surgical intervention. Surgical mortality was defined as the 30-day in hospital mortality. Recurrence rates following surgery are estimated at 2%.[20, 23] The risk of a complicated recurrence requiring emergency surgery after previous elective surgery was estimated 0.5%.[23] Persisting abdominal symptoms after elective surgery was considered to be associated with a four times higher risk of recurrence.[14, 23]

Emergency surgery

Weighted averages of morbidity, mortality and chance of stoma formation after emergency surgery are given in *Table 1*.[12, 24, 25] Primary resection with anastomosis and protecting ileostomy is favored over a Hartmann's procedure in patients with Hinchey III/IV perforated diverticulitis.[26, 27] Only acute complications of ACD requiring surgical intervention (e.g., Hartmann's procedure, resection with primary anastomosis with or without defunctioning ileostomy) were considered in the model. Definitions for major morbidity and mortality in elective surgery were also used for emergency surgery. The chance of stoma formation included both patients with Hartmann's procedure and patients with primary anastomosis and defunctioning ileostomies.[27]

Reversal operation

It was estimated that approximately 60% of the patients with a Hartmann's procedure would be candidates for a reversal operation.[28] Since data on loop ileostomy or colostomy take down in diverticulitis is limited, only Hartmann's reversal was considered in the model, with its own chance of morbidity and mortality.[25, 28] (*Table 1*)

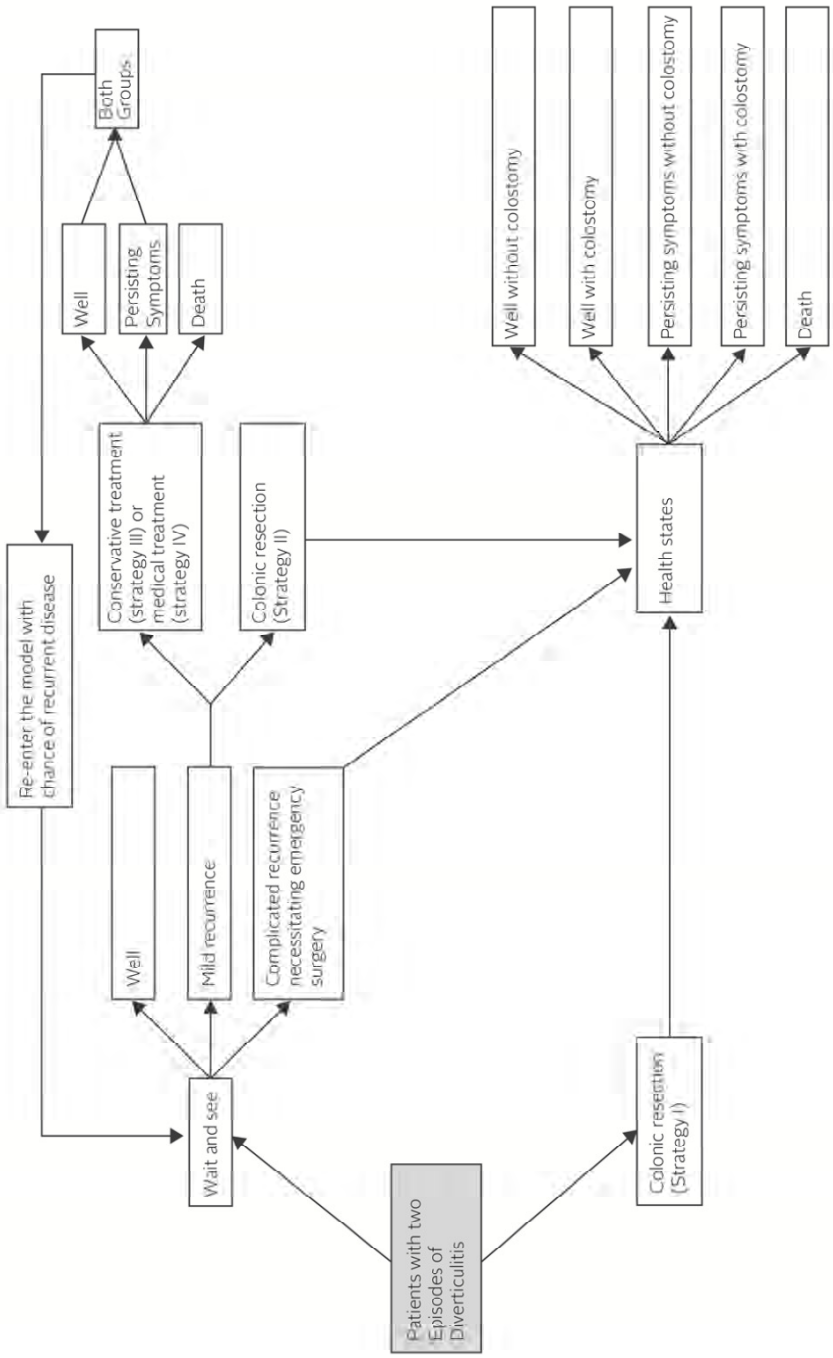


Figure 1: Simplified version of the Markov model

Table 1: Weighted estimates of probabilities and threshold values from one-way sensitivity analysis used in the Markov model

Variable	Baseline value (%)	Range from references (%)	References	Threshold value (%)***	Sensitive	ß-Distribution parameters (α;ß)***
Elective surgery						
- morbidity	16	1.5-36	20-22	NT	N	3.84; 19.89
- mortality	1.5	0-3	20-22	0.1	Y	15.16; 985.24
- stoma formation	5	0-9	20-22	NT	N	5.32; 102.58
- recurrence mild	4	0-8	20, 23	NT	N	NA
- recurrence complicated	0.5	0-1	20, 23	NT	N	NA
- persistent pain	20	10-30	14, 23	NT	N	20.89; 83.94
Emergency surgery						
- morbidity	40	11-51	12, 24, 25	NT	N	20.54; 31.22
- mortality	14	18-21	12, 24, 25	NT	N	14.61; 90.75
- stoma formation	47	45-61	26, 27	NT	N	44.97; 50.37
- recurrence mild	4	0-8	20, 23	NT	N	NA
- recurrence complicated	0.5	0-1	20, 23	NT	N	NA
- persistent pain	20	10-30	20, 23	NT	N	20.89; 83.94
Conservative treatment (flares of diverticulitis only)						
- morbidity*	-	-	-	NA	NA	NA
- mortality	0.5	0-1	8-11, 15	NT	N	NA
- recurrence mild	20	9-29	8-11, 15	NT	N	NA
- recurrence complicated	5.5	3-8	9-11, 15	NT	N	NA
- persistent pain	30	10-40	14, 15, 19	NT	N	24.90; 58.10
Medical treatment (intermittent 5-ASA and non-absorbable antibiotic)						
- morbidity*	-	-	-	NA	NA	NA
- mortality	0.5	0-1	6, 17, 18	NT	N	NA
- recurrence mild	20	9-29	6, 8, 9, 17-19	NT	N	NA
- recurrence complicated	5.5	3-8	6, 9, 11-15, 17, 18	NT	N	NA
- persistent pain	10	5-20	6, 16, 17	73.1**	Y	9.90; 89.10
Hartmann reversal						
- morbidity	47	44-50	25, 28, 31	NA	NA	195.89; 221.45
- mortality	11	2-13	25, 28, 31	NA	NA	10.78; 86.07
Duration of simulation (years)	10 years	5-25 years	-	NT	N	NA

* Morbidity of medical treatment is defined as patients with persistent abdominal complaints after medical treatment and not directly compared in the Markov to surgical morbidity that can only arise in the medical treatment strategy from patients with recurrences requiring emergency surgery. Medical morbidity is corrected for in the Markov model with the different utilities for symptomatic and asymptomatic patients.

** Reduction (%) in probability of persistent pain

*** A number of probabilities in the model were dependent of a specific parameter or event. In a situation in which the probability of a recurrence dependent on the number of recurrences that already occurred for that specific patient, the probability used in the model was extracted from a table. In such a table, a number of different probabilities is available that belong to different numbers of already occurred recurrences. Tables make the model more realistic, but using tables also has some disadvantages. Variables for which the values are extracted from a table can't be used in a sensitivity analysis; neither in a one-way sensitivity analysis, nor in a probabilistic sensitivity analysis.

N = No

Y = Yes

NT = No threshold

NA = Not applicable

Utilities

The utilities assigned to the different health states are summarized in *Table 2*. A utility of 1 was used for a patient who was well without a colostomy after recurrent episodes of diverticulitis. A utility of 0 was assigned to all health states with the outcome death. Patients who remain well but with a colostomy were given a utility of 0.8. This was based on a previously published assessment done in colostomy patients combined with a report on patients with non-cancer colostomies.[29, 30] Patients with persisting abdominal pain but without a colostomy had a utility of 0.95, and patients with persisting abdominal pain and a colostomy a utility of 0.75.[31] To model the decrease in quality of life associated with chronic medication use, we considered a disutility of 0.005 in patients taking maintenance therapy with a non-absorbable antibiotic and 5-ASA.[32] To model the decrease in quality of life associated with an episode of diverticulitis, we considered a loss of 0.042 QALYs (two weeks) for each recurrence.

Sensitivity analysis

One-way deterministic sensitivity analyses were performed for each variable in the model and for utility states, discount rate, and disutility associated with chronic medication use and the duration of simulation if applicable, over their plausible range. The purpose of the one-way sensitivity analysis was to determine which variables, according to the ranges in literature, would affect outcome. If the outcome of the model did not change considerably when the variable was changed, the model was not sensitive to that variable and no threshold was identified. If changing the variable would lead to a different outcome of the model, the model was considered sensitive to that variable and the value to which the optimal strategy changed was considered to be the threshold value for that variable. In order to check the influence of the uncertainty in all variables in the model together, we also performed a probabilistic sensitivity analysis (Monte Carlo simulation). Beta distributions were assumed for proportions and disutilities. Future health is often considered to be less valuable than immediate health. This was handled in the model by discounting future utility with 0.015.

Results

Table 3 summarizes the measured QALYs for all four competing strategies. Over a ten-year period, the strategy colonic resection after two episodes of diverticulitis was associated with the lowest quality-adjusted survival of 8.66 QALY. The strategies colonic resection or conservative treatment or medical treatment after the third episode of diverticulitis were comparable in terms of quality-adjusted survival, 8.78 QALYs, 8.76 QALYs and 8.74 QALYs, respectively. Over a twenty-year period, no change in the optimal treatment strategy was found based on one-way sensitivity analysis. (*Table 1*)

Table 2: State utilities and threshold values from one-way sensitivity analysis used in the Markov model

Health state	Utility estimate	Range	References	Threshold value *	Sensitive	ß-Distribution parameters* (α;ß)
Well without stoma	1.00	-	-	NA	NA	NA
Well with stoma	0.80	0.20-1.00	29,30	NT	N	156.75; 39.17
Persisting abdominal pain without stoma	0.95	0.50-1.00	29	0.82	Y	192.67; 10.21
Persisting abdominal pain with stoma	0.75	0.40-1.00	30,31	NT	N	158.07; 52.46
Death	0	-	-	NA	NA	NA
Disutilities	**Disutility**					
Chronic medication use	0.005	0-0.04	32	NT	N	0.057; 11.38
Discount rate	0.05	0-0.1	-	NT	N	3.75; 71.25

* A number of probabilities in the model were dependent of a specific parameter or event. In a situation in which the probability of a recurrence dependent on the number of recurrences that already occurred for that specific patient, the probability used in the model was extracted from a table. In such a table, a number of different probabilities is available that belong to different numbers of already occurred recurrences. Tables make the model more realistic, but using tables also has some disadvantages. Variables for which the values are extracted from a table can't be used in a sensitivity analysis.
Y = Yes
NT = No threshold
NA = Not applicable

Mortality

Overall mortality for each strategy is summarized in *Table 3*. Overall mortality, e.g., 30-day in hospital surgical mortality and mortality based on age-specific mortality rates, was comparable between the strategies colonic resection, conservative treatment and medical treatment after the third episode of diverticulitis, 7.8%, 7.6% and 7.6%, respectively. The 30-day in hospital surgical mortality in the strategy colonic resection after two episodes of diverticulitis was 1.4% with 8.4% overall mortality. The lower QALYs generated by the elective surgery strategy after two episodes is mainly caused by this early mortality risk. This effect was also notable through one-way sensitivity analysis. At a probability of mortality for elective surgery less than 0.1%, elective surgery became the dominant strategy. (*Figure 2*)

Table 3: Results of base case analysis for patients who suffered from two episodes of diverticulitis

	STRATEGY			
	I Colonic resection after two episodes of diverticulitis	**II Colonic resection after three episodes of diverticulitis**	**III Conservative treatment after three episodes of diverticulitis (flares of diverticulitis only)**	**IV Medical treatment after three episodes of diverticulitis (5-ASA and rifaximin)**
QALYs*	8.66	8.78	8.76	8.74
Overall mortality	8.4%	7.8%	7.6%	7.6%
Stoma formation	1.1%	0.7%	0.9%	0.9%
Mild recurrence	3.5%	5.3%	8.9%	8.7%
Severe recurrence	1.1%	2.4%	5.2%	5.2%
Persistent complaints	18.2%	18.5%	18.4%	14.7%

* QALYs: Quality Adjusted Life Years

Stoma formation and recurrences

The chance of stoma formation and chance of a mild or severe recurrence for each strategy are summarized in *Table 3*. The strategy colonic resection after two episodes of diverticulitis had the highest chance of stoma formation (1.1%); most enterostomies are made due to complications after surgical resection. The conservative and medical treatment strategies had a 0.9% chance of stoma formation, all caused by patients with a severe recurrence necessitating emergency surgery. The strategy colectomy after the third episode of diverticulitis, had the lowest overall chance of stoma formation (0.7%).

The chance of a mild recurrence was the highest for the conservative (8.9%) and medical (8.7%) treatment strategies, and the lowest for the strategy colectomy after two episodes of diverticulitis (3.5%). The number of severe recurrences necessitating emergency surgery was the lowest for the strategy colectomy after two episodes of diverticulitis (1.1%) and the highest for the conservative and medical treatment strategies (5.2%).

Persistent symptoms

The chance of persistent symptoms after each strategy is summarized in *Table 3*. The lowest rate of persistent abdominal symptoms was observed in the medical treatment strategy (14.7%). The other three strategies were comparable in terms of persistent abdominal symptoms, varying between 18.2% and 18.5%. Sensitivity analysis revealed a change in strategy in favor of medical treatment, in case a reduction of 73% of abdominal symptoms would be achieved by medical treatment (*Figure 2*) or if the utility of persistent abdominal symptoms in patients with a stoma was less than 0.82.

Sensitivity analysis

Probabilistic sensitivity analysis demonstrated that the strategies colonic resection, conservative or medical treatment after the third episode of diverticulitis were comparable across the full range of variables in the model with a mean QALY of 8.78 (sd = 0.052), 8.77 (sd = 0.053) and 8.74 (sd = 0.049), respectively. The range of QALYs for these three strategies overlaps completely. (*Figure 3*, *Table S1*) Elective surgery consistently generated a lower mean QALY of 8.66 (sd = 0.071) across the full range of variables in the model. Considering the results found by the one-way sensitivity analysis this is caused by an early mortality risk of surgery.

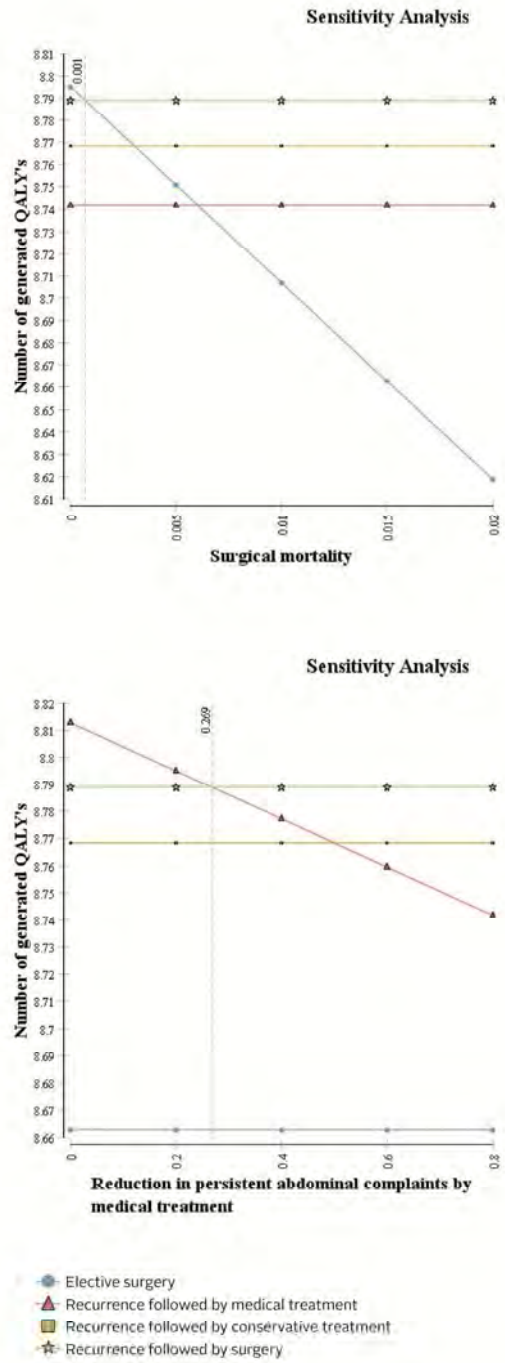


Figure 2: One-way sensitivity analysis on surgical mortality and reduction of persistent abdominal complaints with medical treatment

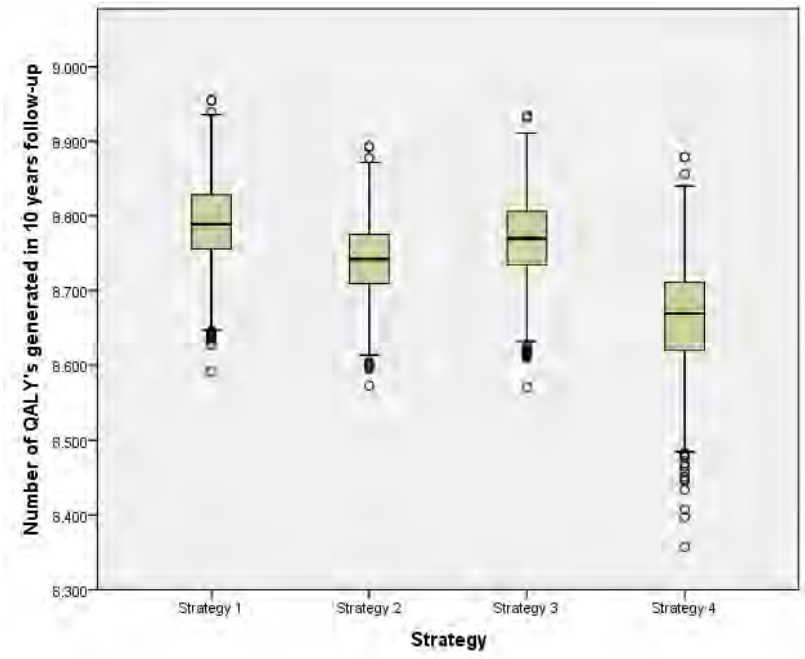


Figure 3: Boxplot with the results of generated QALYs in ten years for all the four treatment strategies with Monte Carlo simulation (probabilistic sensitivity analysis)

Discussion

Although persistent abdominal symptoms are increasingly recognized as a paramount problem in post-diverticulitis patients, we could not adequately define these patients because of large heterogeneity in persistent abdominal symptoms. Abdominal symptoms in conservatively treated diverticulitis may reflect visceral hypersensitivity.[19] After surgery these may be related to a shorter bowel (increased bowel movements), to a stenosis of the anastomosis (obstructive signs) or a stoma presence (leakage).

Timing of elective colectomy has been previously studied in two Markov models.[38, 39] Both studies differed in modeling approach but showed comparable results regarding (early) colectomy. Our imputed data in the Markov model was based on the most recent literature, embedding pivotal changes in both surgical and medical treatment of recurrent disease from the last ten years. In addition, persistent abdominal symptoms were incorporated, which occur in one of six patients and are indispensable for accurate determining of quality-adjusted survival.

Recurrent episodes of diverticulitis mostly run a benign course; only 5.5% of patients with recurrent hospitalizations for diverticulitis have emergency surgery.[10, 11] Most patients presenting with complicated diverticulitis do so at the time of their first attack.[12] Based on these findings a shift towards a conservative treatment in patients with recurrent diverticulitis was proposed albeit that elective surgery still is routine practice in many countries.[4, 8, 12] Notably, an increase of elective resection for diverticulitis is reported especially in young patients.[40]

Although a Markov model is a helpful tool, it has a few limitations. The probability of each outcome is based on results from previous studies. A recent systematic review of surgery for diverticulitis revealed that the overall quality of studies is low.[33] Utilities could not be derived directly from individuals with diverticulitis but from limited comparable studies of patients with other benign colonic diseases. This was believed to be acceptable for utilities including an enterostomy because stomas significantly impair QoL scores.[41] Altering the range of utilities over their plausible range, only affected the results of the decision analysis in patients with persistent abdominal complaints without a stoma. Best would be to have utilities based on patient reported outcomes (PROs), but studies are scarce that report on PROs in patients with diverticulitis.

Elective surgery after two episodes of diverticulitis should be questioned as primary treatment option for recurrent diverticulitis. Surgeons should not operate at quite the rate they have been trained to think. The model has limitations when the individual patient and physician face a complex decision, particularly a young patient with large disease burden. A patient-oriented decision aid using data from this analysis would be a valuable tool to facilitate shared decision making for treatment of recurrent diverticulitis.

Reference list

1 Ritz JP, Gröne J, Engelmann S, Lehmann KS, Buhr HJ, and Holmer C. [What is the actual benefit of sigmoid resection for acute diverticulitis? : Functional outcome after surgical and conservative treatment]. Chirurg. 2013, Aug;84(8):673-80.

2 Pasternak I, Wiedemann N, Basilicata G, and Melcher GA. Gastrointestinal quality of life after laparoscopic-assisted sigmoidectomy for diverticular disease. Int J Colorectal Dis. 2012, Jun;27(6):781-7.

3 Strate LL, Modi R, Cohen E, and Spiegel BM. Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights. Am J Gastroenterol. 2012, Oct;107(10):1486-93.

4 Rafferty J, Shellito P, Hyman NH, Buie WD, and Standards Committee of American Society of Colon and Rectal Surgeons. Practice parameters for sigmoid diverticulitis. Dis Colon Rectum. 2006, Jul;49(7):939-44.

5 Andeweg CS, Mulder IM, Felt-Bersma RJ, Verbon A, van der Wilt GJ, van Goor H, et al. Guidelines of Diagnostics and Treatment of Acute Left-Sided Colonic Diverticulitis. Dig Surg. 2013, Aug 20;30(4-6):278-292.

6 Tursi A, Di Mario F, Brandimarte G, Elisei W, Picchio M, Loperfido S, et al. Intermittent versus every-day mesalazine therapy in preventing complications of diverticular disease: a long-term follow-up study. Eur Rev Med Pharmacol Sci. 2013, Dec;17(23):3244-8.

7 Tursi A. New physiopathological and therapeutic approaches to diverticular disease of the colon. Expert Opin Pharmacother. 2007, Feb;8(3):299-307.

8 Broderick-Villa G, Burchette RJ, Collins JC, Abbas MA, and Haigh PI. Hospitalization for acute diverticulitis does not mandate routine elective colectomy. Arch Surg. 2005, Jun;140(6):576-81; discussion 581-3.

9 Biondo S, Parés D, Martí Ragué J, Kreisler E, Fraccalvieri D, and Jaurrieta E. Acute colonic diverticulitis in patients under 50 years of age. Br J Surg. 2002, Sep;89(9):1137-41.

10 Li D, de Mestral C, Baxter NN, McLeod RS, Moineddin R, Wilton AS, and Nathens AB. Risk of readmission and emergency surgery following nonoperative management of colonic diverticulitis: a population-based analysis. Ann Surg. 2014, Sep;260(3):423-30; discussion 430-1.

11 Anaya DA, and Flum DR. Risk of emergency colectomy and colostomy in patients with diverticular disease. Arch Surg. 2005, Jul;140(7):681-5.

12 Chapman JR, Dozois EJ, Wolff BG, Gullerud RE, and Larson DR. Diverticulitis: a progressive disease? Do multiple recurrences predict less favorable outcomes? Ann Surg. 2006, Jun;243(6):876-830; discussion 880-3.

13 Chautems RC, Ambrosetti P, Ludwig A, Mermillod B, Morel P, and Soravia C. Long-term follow-up after first acute episode of sigmoid diverticulitis: is surgery mandatory?: a prospective study of 118 patients. Dis Colon Rectum. 2002, Jul;45(7):962-6.

14 Bargellini T, Martellucci J, Tonelli P, and Valeri A. Long-term results of treatment of acute diverticulitis: still lessons to be learned? Updates Surg. 2012, Dec 28;

15 Chabok A, Påhlman L, Hjern F, Haapaniemi S, Smedh K, and AVOD Study Group. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg. 2012, Apr;99(4):532-9.

16 Parente F, Bargiggia S, Prada A, Bortoli A, Giacosa A, Germanà B, et al. Intermittent

treatment with mesalazine in the prevention of diverticulitis recurrence: a randomised multicentre pilot double-blind placebo-controlled study of 24-month duration. Int J Colorectal Dis. 2013, Oct;28(10):1423-31.

17 Maconi G, Barbara G, Bosetti C, Cuomo R, and Annibale B. Treatment of Diverticular Disease of the Colon and Prevention of Acute Diverticulitis: A Systematic Review. Dis Colon Rectum. 2011, Oct;54(10):1326-1338.

18 Raskin JB, Kamm MA, Jamal MM, Márquez J, Melzer E, Schoen RE, et al. Mesalamine did not prevent recurrent diverticulitis in phase 3 controlled trials. Gastroenterology. 2014, Oct;147(4):793-802.

19 Simpson J, Neal KR, Scholefield JH, and Spiller RC. Patterns of pain in diverticular disease and the influence of acute diverticulitis. Eur J Gastroenterol Hepatol. 2003, Sep;15(9):1005-10.

20 Jones OM, Stevenson AR, Clark D, Stitz RW, and Lumley JW. Laparoscopic resection for diverticular disease: follow-up of 500 consecutive patients. Ann Surg. 2008, Dec;248(6):1092-7.

21 Klarenbeek BR, Samuels M, van der Wal MA, van der Peet DL, Meijerink WJ, and Cuesta MA. Indications for elective sigmoid resection in diverticular disease. Ann Surg. 2010, Apr;251(4):670-4.

22 Gervaz P, Mugnier-Konrad B, Morel P, Huber O, and Inan I. Laparoscopic versus open sigmoid resection for diverticulitis: long-term results of a prospective, randomized trial. Surg Endosc. 2011, Oct;25(10):3373-8.

23 Andeweg C, Peters J, Bleichrodt R, and van Goor H. Incidence and risk factors of recurrence after surgery for pathology-proven diverticular disease. World J Surg. 2008, Jul;32(7):1501-6.

24 Binda GA, Karas JR, Serventi A, Sokmen S, Amato A, Hydo L, et al. Primary anastomosis vs nonrestorative resection for perforated diverticulitis with peritonitis: a prematurely terminated randomized controlled trial. Colorectal Dis. 2012, Nov;14(11):1403-10.

25 Gooszen AW, Gooszen HG, Veerman W, Van Dongen VM, Hermans J, Klien Kranenbarg E, and Tollenaar RA. Operative treatment of acute complications of diverticular disease: primary or secondary anastomosis after sigmoid resection. Eur J Surg. 2001, Jan;167(1):35-9.

26 Abbas S. Resection and primary anastomosis in acute complicated diverticulitis, a systematic review of the literature. Int J Colorectal Dis. 2007, Apr;22(4):351-7.

27 Constantinides VA, Tekkis PP, Athanasiou T, Aziz O, Purkayastha S, Remzi FH, et al. Primary resection with anastomosis vs. Hartmann's procedure in nonelective surgery for acute colonic diverticulitis: a systematic review. Dis Colon Rectum. 2006, Jul;49(7):966-81.

28 Salem L, Anaya DA, Roberts KE, and Flum DR. Hartmann's colectomy and reversal in diverticulitis: a population-level assessment. Dis Colon Rectum. 2005, May;48(5):988-95.

29 Boyd NF, Sutherland HJ, Heasman KZ, Tritchler DL, and Cummings BJ. Whose utilities for decision analysis? Med Decis Making. 1990;10(1):58-67.

30 Krouse R, Grant M, Ferrell B, Dean G, Nelson R, and Chu D. Quality of life outcomes in 599 cancer and non-cancer patients with colostomies. J Surg Res. 2007, Mar;138(1):79-87.

31 Bolster LT, and Papagrigoriadis S. Diverticular disease has an impact on quality of life -- results of a preliminary study. Colorectal Dis. 2003, Jul;5(4):320-3.

32 Saini SD, Waljee AK, and Higgins PD. Cost utility of inflammation-targeted therapy for patients with ulcerative colitis. Clin

Gastroenterol Hepatol. 2012, Oct;10(10):1143-51.
33 Regenbogen SE, Hardiman KM, Hendren S, and Morris AM. Surgery for Diverticulitis in the 21st Century: A Systematic Review. JAMA Surg. 2014, Jan 15;
34 Stollman N, Magowan S, Shanahan F, Quigley EM, and DIVA Investigator Group. A randomized controlled study of mesalamine after acute diverticulitis: results of the DIVA trial. J Clin Gastroenterol. 2013, Aug;47(7):621-9.
35 Kruis W, Meier E, Schumacher M, Mickisch O, Greinwald R, Mueller R, and German SAG-20 Study Group. Randomised clinical trial: mesalazine (Salofalk granules) for uncomplicated diverticular disease of the colon--a placebo-controlled study. Aliment Pharmacol Ther. 2013, Apr;37(7):680-90.
36 Brandimarte G, and Tursi A. Rifaximin plus mesalazine followed by mesalazine alone is highly effective in obtaining remission of symptomatic uncomplicated diverticular disease. Med Sci Monit. 2004, May;10(5):PI70-3.
37 Tursi A, Brandimarte G, Giorgetti GM, and Elisei W. Mesalazine and/or Lactobacillus casei in preventing recurrence of symptomatic uncomplicated diverticular disease of the colon: a prospective, randomized, open-label study. J Clin Gastroenterol. 2006, Apr;40(4):312-6.
38 Richards RJ, and Hammitt JK. Timing of prophylactic surgery in prevention of diverticulitis recurrence: a cost-effectiveness analysis. Dig Dis Sci. 2002, Sep;47(9):1903-8.
39 Salem L, Veenstra DL, Sullivan SD, and Flum DR. The timing of elective colectomy in diverticulitis: a decision analysis. J Am Coll Surg. 2004, Dec;199(6):904-12.
40 Etzioni DA, Mack TM, Beart RW, and Kaiser AM. Diverticulitis in the United States: 1998-2005: changing patterns of disease and treatment. Ann Surg. 2009, Feb;249(2):210-7.
41 Sjödahl R, Schulz C, Myrelid P, and Andersson P. Long-term quality of life in patients with permanent sigmoid colostomy. Colorectal Dis. 2012, Jun;14(6):e335-8.

Full search description to obtain the probabilities of clinical events (supplemental material)

A Pubmed, Medline and Embase database search was conducted of articles published from January 1970 till June 2014 relevant to the subject of diverticulitis, using the following keywords and MeSH terms: [“Diverticulitis”[MeSH] OR “Diverticulitis, Colonic”[MeSH] OR (“Diverticulum AND “Inflammation”) OR (“Diverticulosis, Colonic” AND “Inflammation”[MesH] OR “natural history“, OR “Recurrence”[MesH] OR “abdominal complaint” OR “abdominal symptoms” OR “Chronic Pain[Mesh]” OR “SUDD” OR “Surgery”[Subheading] OR “medical treatment” OR “Therapy”[Subheading] OR “Treatment outcome”[MesH]” OR “antibiotics” OR “probiotics” OR “Anti-bacterial agents”[MesH] or “5-ASA”[MesH] OR “Mesalamine”[MesH]. The search strategies were adapted to the different databases to maximize yield. Additionally, all selected studies were reviewed for cross-references. Data were extracted from systematic reviews and meta-analysis, Randomised Controlled Trials (RCTs) and cohort studies with a minimal follow-up of three months and more than 50 patients. The following inclusion criteria were applied: adults with every stage diverticulitis; conservative and/or operative treatment and/or reporting on chronic abdominal pain or abdominal symptoms. A weighted mean was obtained for each variable and used as the baseline estimate, taking into account the number of patients that contributed to each outcome by each data source. Furthermore, the data extracted from the literature was used to obtain ranges for sensitivity analysis. (*Table 1*)

Table S1: Results of generated QALYs for each strategy after probabilistic sensitivity analysis (Monte Carlo simulation)

Strategy		Descriptive statistics				
		N	Minimum	Maximum	Mean	Standard deviation
I	Generated QALYs: Colonic resection after two episodes of diverticulitis	1000	8.35	8.87	8.66	0.071
II	Generated QALYs: Colonic resection after three episodes of diverticulitis	1000	8.59	8.95	8.78	0.052
III	Generated QALYs: Conservative treatment after three episodes of diverticulitis	1000	8.57	8.93	8.77	0.053
IV	Generated QALYs: Medical treatment after three episodes of diverticulitis	1000	8.57	8.89	8.74	0.047

Chapter 7

Patient reported outcomes in diverticulitis: a systematic review and meta-analysis

Caroline Andeweg

Rosalyn Berg

Bart Staal

Richard ten Broek

Harry van Goor

Submitted

Abstract

Background and aims

Patients with diverticulitis may develop multiple recurrences and chronic abdominal complaints. Recurrent diverticulitis is seldom complicated, which has led to a shift towards conservative treatment. However, some studies suggest that surgical intervention reduces the burden of recurrent disease and persistent abdominal complaints. We conducted a systematic review and meta-analysis of Quality of Life (QoL) and other Patient-Reported Outcomes (PROs) following conservative and surgical treatments for diverticulitis.

Methods

CENTRAL, MEDLINE, EMBASE, and Psycinfo were searched for randomized trials and cohort studies reporting on QoL or other PROs after conservative or operative treatment for any stage of diverticulitis from January 1990 to May 2014. Eight PROs were defined and graded according to their clinical relevance. Risk of bias was assessed using the Cochrane Collaboration tool. Subgroup and sensitivity analyses were performed to test the robustness of the results. The review protocol was registered through PROSPERO (CRD42013005854).

Results

Thirty-four studies (3,670 patients) were selected; each had a high risk of bias. Patients reported better general QoL after elective laparoscopic colonic resection short form (SF) 36 score (78.3, 95% confidence interval [CI]: 70.5-86.2) than after conservative treatment (58.1, 95% CI: 47.2-69.1), but the difference was not reproduced in studies with head-to-head comparisons. Gastrointestinal QoL was comparable between the treatments. One third of the patients reported chronic abdominal pain following both treatment types. Gastrointestinal symptoms were less frequent following laparoscopic surgery when compared with conservative treatment, among all cohorts (9% [95% CI: 4-14%] vs. 36% [95% CI: 27-45%]), and in one trial directly comparing both treatments (odds ratio: 0.35, 95% CI: 0.16-0.7).

Conclusions

Elective laparoscopy for recurrent diverticulitis results in better general QoL and gastrointestinal symptoms compared with conservative treatment. Almost one third of patients have gastro-intestinal complaints after undergoing treatment for diverticulitis. There is a further need for high-quality trials regarding PROs in diverticulitis.

Keywords

Diverticulitis; Quality of Life; Patient Reported Outcomes; treatment; systematic review; meta-analysis

Introduction

Diverticular disease of the sigmoid and descending colon is a common condition in Western countries. It is present in more than 50% of individuals at the age of 65 years. The prevalence steadily increases with advancing age to around 65% at the age of 85.[1, 2] An estimated 10-25% of patients with diverticulosis develop one or more episode of diverticulitis during their lifetime.[3, 4] Uncomplicated diverticulitis occurs when inflammation of one or more diverticulum leads to an inflammatory process without perforation or abscess formation.[5] Episodes of uncomplicated diverticulitis often involve abdominal pain, mild fever, flatulence, and constipation. An episode of complicated acute diverticulitis is associated with abscess formation or perforation. Complicated diverticulitis is relatively rare and occurs in approximately 10% of patients with diverticulitis.[6, 7] Complicated diverticulitis is associated with high rates of morbidity and mortality and often requires percutaneous drainage of abscesses or emergent surgery in the event of purulent or faecal peritonitis secondary to perforation of the colon.

Uncomplicated recurrent diverticulitis can be treated by conservative means or by surgery. Recent epidemiological data show that recurrent episodes of diverticulitis are seldom complicated, which has led to a marked shift from surgical treatment towards conservative treatment.[8-11] Although conservative treatment is often satisfactory and avoids the risks of complications and mortality associated with elective surgery, approximately 25% of patients suffer from additional episodes of diverticulitis.[12-14] Surgery for diverticulitis has become less invasive and safer.[15] Some evidence suggests that surgical intervention reduces the burden of recurrent disease and chronic abdominal complaints.[16-18]

Early symptom relief and complications associated with the treatment are the primary outcomes reported in most studies of the treatment of diverticulitis. The patients' perspectives on recurrences and persistent bowel symptoms associated with the treatment are seldom reported, which is surprising considering the large health burden, the recurrent and chronic character, and the controversies associated with the treatment of diverticulitis.[11, 19]

Quality of Life (QoL) and other Patient Reported Outcomes (PROs) are increasingly recognized as relevant clinical outcomes after medical interventions, especially in chronic disease.[20, 21] The effects of conservative or operative treatment for (recurrent) diverticulitis on QoL and PROs are not clear, which prompted us to undertake a systematic review and meta-analysis of studies addressing QoL and other PROs after conservative or operative treatment for diverticulitis. The results of this study will help doctors and patients to make informed decisions when choosing between conservative and operative treatments in cases of recurrent diverticulitis.

Materials and methods

Search strategy and selection criteria

Two researchers (CSA and RB) searched entries in the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and Psycinfo made from January 1990 to May 25, 2014. Searches included the following MeSH descriptors: “Diverticulitis”, “Diverticulitis, Colonic”, (“Diverticulum” AND “Inflammation”), (“Diverticulosis, Colonic” AND "Inflammation”[Mesh]), “Quality of Life”, “Health Status”, “Questionnaires”, “Symptom Assessment”, “Defecation”, “Chronic Pain”, “Pain Measurement”, “Faecal Incontinence”, “Disability Evaluation”, “Activities of Daily Living”, “Return to Work”, and “Satisfaction”. For a full description of the search strategy, see *Appendix A*. Additionally, we searched the reference lists of relevant studies and previous reviews. Grey literature was searched using Open SIGLE, Scientific Web Plus, and ‘Grey literature available in the Netherlands’. Trial registers were searched (International Clinical Trials Registry Platform and the UK Clinical Trials Gateway) for relevant records of unpublished trials. No language restrictions were applied. We carried out the review in accordance with a protocol that was registered in PROSPERO (CRD42013005854).

Studies were retrieved and selected by two independent reviewers (CSA and RB) in two rounds, first based on the title and abstract and then based on the full text measured against pre-specified criteria. Randomized Controlled Trials (RCTs) and cohort studies with a minimal follow-up of three months were considered eligible for inclusion. Studies that included adults with any stage of diverticulitis, conservative and/or operative treatment of diverticulitis, and reports of QoL or other PROs were selected (*Table S1*). Studies reporting on colorectal surgery for a variety of indications were excluded if we could not extract separate results for the cohort of patients with diverticulitis.

Data extraction

Two reviewers (RB and RPGtB) extracted and checked the data. We extracted information on the study design, patient characteristics, the number of participants, and the outcomes reported. Any discrepancies were resolved by discussion or by a third reviewer (CSA). If the dataset was incomplete, the authors were contacted by e-mail for the missing data.

Outcome measures were extracted from the literature. Eight PROs were defined and graded by clinical relevance (critical for decision-making, important for decision-making, or of limited importance), as suggested by the GRADE working group.[22] PROs critical for decision-making included gastrointestinal QoL, based on answers to the Gastrointestinal Quality of Life Index (GIQLI), and general QoL, based on the Short Form (36) Health Survey (SF-36), the European Organisation for Research and the Treatment of Cancer quality of life survey (EORTC), and the Cleveland Global Quality of Life instrument (CGQL). Disability (defined as an inability to perform the activities of daily living, physical activities, and the activities necessary to return to work) was also graded as critical for decision-making.

Chronic abdominal pain, faecal incontinence, and patient satisfaction were graded as PROs important for decision-making. Chronic abdominal pain was defined as the persistence of abdominal pain after three months of follow-up. Studies that used a visual analogue scale to score pain were included. Faecal incontinence was assessed either on a faecal incontinence scale or by the percentage of patients who complained of incontinence. Patient satisfaction was assessed either by a satisfaction score or as the percentage of patients expressing good to excellent satisfaction with the treatment.

The PROs of limited clinical relevance were persistent bowel symptoms (i.e., hypogastric pain or bloating, diarrhea, constipation, flatulence, painful defecation, and rectal bleeding) and urogenital symptoms (i.e., erectile dysfunction, ejaculation difficulties, diminished libido, and urinary and sexual dysfunction; *Table 1*).

Table 1: Patient-reported outcomes ranked according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) by relevance according to the patients' perspective

Grading		**Outcomes**
Critical for decision-making	⊕⊕⊕	Gastro-intestinal quality of life [Π]
	⊕⊕⊕	General quality of life [Σ]
	⊕⊕⊕	Disability
Important for decision-making	⊕⊕	Chronic abdominal pain
	⊕⊕	Faecal incontinence
	⊕⊕	Patient satisfaction
Limited importance	⊕	Persistent bowel symptoms
	⊕	Urinary/sexual function

[Π] Gastro-intestinal quality of life, measured by the Gastro Intestinal Quality of Life Index (GIQLI) questionnaire
[Σ] General quality of life assessed by the Short Form 36 Health Survey questionnaire (SF-36), The European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-C 30 (EORTC QLQ-C30), and/or the Cleveland Global Quality of Life instrument (CGQL)

Risk-of-bias assessment

Two reviewers (CSA and RB) independently assessed the methodological quality of the retrieved articles. Any discrepancies were resolved by discussion or by a third reviewer (RPGtB). The Cochrane Collaboration's tool for the assessment of bias risk was used to assess the risk of systematic error.[23] Seven components associated with the risk of bias were assessed: the generation of the allocation sequence, the allocation concealment, the blinding of participants, the masking of outcome assessors, selective outcome reporting, incomplete follow-up, and other potential sources of bias. The incomplete follow-up component was considered adequate if fewer than 10% of the patients were lost to follow-up and a description of the loss was provided. Trials in which one or more of the seven components had a high score or was unclear were defined as having a high risk of bias. Heterogeneity among baseline characteristics, clinically suspected diverticulitis

without radiological confirmation, and premature trial stoppage were considered as other biases.

Data analysis and presentation

The inverse variance method for the pooling of prevalence and continuous data was used. The Mantel-Haenszel method was applied for the pooling of dichotomous data, and the results were presented as the Relative Risk (RR) with 95% Confidence Interval (CI). A *p*-value <0.05 was considered statistically significant. Heterogeneity was explored using I^2 tests, as recommended by the Cochrane Handbook for Systematic Reviews of Intervention. An I^2 value between 50% and 75% was defined as substantial heterogeneity, and an I^2 value = 75% was defined as considerable heterogeneity. A fixed-effect model was applied for the meta-analysis. In the presence of significant statistical heterogeneity, a random-effects model was used. Data were analyzed using Review Manager 5.0. (Review Manager (RevMan) [Computer program] Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) and R version 2.12.0.

In the primary analyses, only available data were analyzed. The impact of incomplete data was explored through sensitivity analyses using the standard deviation imputed from p-values according to the algorithms in the Cochrane Handbook for Systematic Reviews of Intervention. The median was used when the mean was not available. If it was not possible to calculate the standard deviation from the *p*-value or the CI, the standard deviation was imputed as the highest standard deviation noted for the group and outcome in question.

Subgroup analyses were performed for the study type (trials with low risk of bias vs. trials with high risk of bias), the treatment type (conservative, elective laparoscopic surgery, elective open surgery, emergency surgery, and studies with mixed or unspecified types of surgery), and the diverticulitis type (complicated vs. uncomplicated and first episode vs. recurrent disease).

We followed both the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in reporting the results.

Results

Search results

The search identified 2,075 published articles, 1,306 of which were unique studies. The manual review of the references, grey literature, and trial registers identified an additional 275 studies for abstract evaluation. We excluded 1,491 studies after title and abstract screening and 50 more after full-text review. We extensively reviewed the remaining 40

studies, which included a total of 4,228 patients. Six studies either used unvalidated symptom scores[24, 25] or had incomplete outcome data.[26-28] Consequently, 34 studies comprising 3,670 patients were included in our meta-analyses (*Figure 1*).[14, 16-18, 29-59]

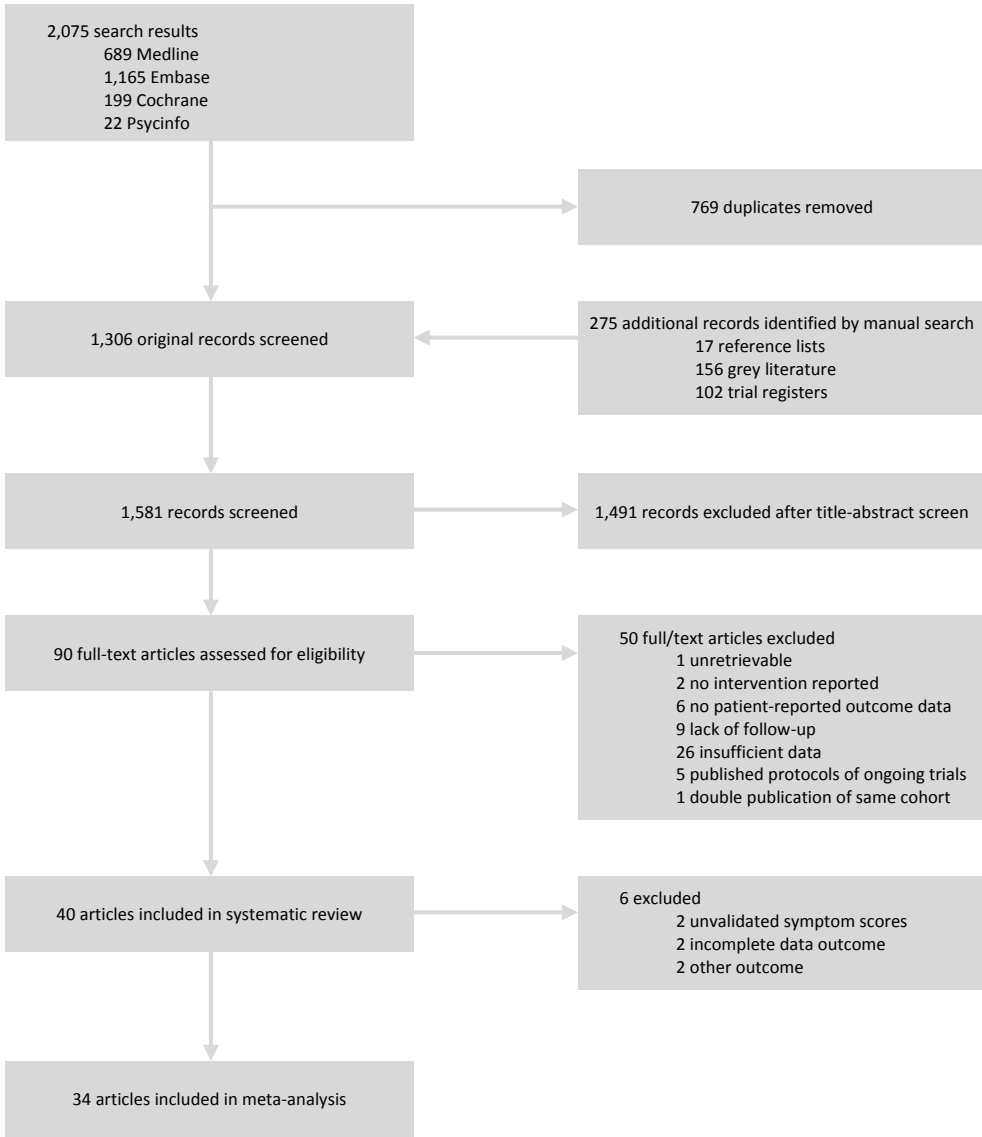


Figure 1: Study selection

Characteristics and quality assessment of the selected studies

Table S1 shows descriptive data for the 40 qualifying studies, and *Figure 2* shows the quality assessment of the selected studies. The inclusion criteria were well documented in most of the studies, but they varied widely. Complicated (symptomatic) diverticular disease and diverticulitis were used interchangeably as terms for the same disorder. The disease severity was staged according to the Hinchey classification in one third of the studies and according to Hansen Stock classification in two studies. Elective surgery was generally performed at least 3 months after the last episode of diverticulitis. Emergency surgery consisted of a single staged or staged resection. All the studies had a high risk of bias in the assessment-of-outcome domain, because the outcome assessors were not blinded or may have been involved in the treatment. Most of the studies failed to describe how the allocation sequence was generated (80% of the studies), adequately conceal the allocation (80% of the studies), or blind the participants or personnel (85% of the studies). More than half of the studies had inadequate follow-up methods and inadequate descriptions of the reasons for loss to follow-up. The risk of outcome bias through selective reporting was high in 80% of the studies. Overall, none of the selected studies had a low risk of bias (*Figure 2*). The eight predefined PROs were distributed unevenly among the studies. *Table 2* summarizes the main findings for each outcome measure, sorted by treatment modality.

Outcomes critical for decision-making

Gastrointestinal QoL was reported in three studies evaluating 237 patients. The mean gastrointestinal QoL, as measured by the GIQLI (range: 0-144), was good, with a mean of 113 (95% CI: 111-116). The type of treatment did not influence the gastrointestinal QoL. General QoL was reported in six studies evaluating 591 patients. The mean SF-36 score (range: 0-100) for patients with diverticulitis was 70.3 (95% CI: 60.5-80.0). The SF-36 score was significantly higher for patients who underwent laparoscopic surgery (mean=78.3; 95% CI: 70.5-86.2) compared with those who underwent conservative treatment (mean=58.1; 95% CI: 47.2-69.1), but the difference was only apparent when comparing cohorts among studies and not in a head-to-head analysis (*Table 3* and *Figure 3*). There was considerable heterogeneity among the results of the different studies (I^2=92%). There was no significant difference in the mean SF-36 score between laparoscopic and open surgery. The type of treatment did not affect the EORTC or CGQL scores (EORTC mean=82.7, 95% CI: 77.2-88.2; CGQL mean=73, 95% CI: 66.6-79.4; *Figure 3*). The prevalence of disability (6%, 95% CI: 2-10%) was reported in one study evaluating 120 patients who had undergone laparoscopic surgery.

Table 2: Summary of the main finding per outcome sorted by treatment modality (all cohorts included)

Outcome	GRADE	Overall	Elective laparoscopic surgery	Elective open surgery	Emergency surgery	Mixed or unspecified surgery	Conservative treatment
Gastrointestinal related QoL	⊕⊕⊕	3 studies; [17,18,29] *n*=237	2 studies; [17,18] *n*=160	1 study; [29] *n*=18	1 study; [29] *n*=9	NA	1 study; [29] *n*=50
- GIQLI score (mean ± 95% CI)		113 (111-116)	114 (111-116)	110 (101-119)	110 (91-129)		109 (102-116)
General QoL	⊕⊕⊕	6 studies; [30-36] *n*=591	4 studies; [31-36] *n*=227	3 studies; [31,34-36] *n*=113	NA	2 studies; [30,32] *n*=193	2 studies; [32,35,36] *n*=58
- SF 36 (mean ± 95% CI)		70.3 (60.5-80.0)	78.3 (70.5-86.2)	67.4 (60.0-74.9)		62.6 (45.7-79.4)	58.1 (47.2-69.1)
- EORTC (mean ± 95% CI)		82.7 (77.2-88.2)	84.3 (79.0-90.0)	80.7 (75.0-86.4)		NA	NA
- CGQL (mean ± 95% CI)*		73.0 (66.6-79.4)	75.0 (69.2-80.8)	72.0 (63.6-80.4)		NA	73.0 (68.7-77.3)
Disability	⊕⊕⊕	1 study; [37] *n*=120	1 study; [37] *n*=120	NA	NA	NA	NA
Prevalence % (95% CI)		6% (2-10%)	6% (2-10%)				
Chronic abdominal pain	⊕⊕	8 studies; [14,35,36,38-43] *n*=1166	2 studies;[39,43] *n*=126	NA	1 study; [39] *n*=58	3 studies; [35,36,38,42] *n*=204	5 studies; [14,39-42] *n*=778
Prevalence % (95% CI)		31% (29-34%)	17% (6-29%)		14% (5-23%)	42% (15-69%)	36% (20-51%)
Faecal incontinence	⊕⊕	4 studies; [16,42,44,45] *n*=543	1 study; [16] *n*=113	1 study; [45] *n*=116	NA	2 studies; [42,44] *n*=282	NA
Prevalence % (95% CI)		9.0% (5-12%)	11% (5-16%)	3% (0-7%)		14% (0-35%)	
Satisfaction	⊕⊕	5 studies; [18,43,46-48] *n*=344	3 studies; [18,43,46] *n*=253	1 study; [47] *n*=64	NA	1 study; [48] *n*=27	NA
Prevalence % (95% CI)		96% (95-98%)	96% (93-98%)	98% (95-100%)		89% (77-100%)	
Gastrointestinal symptoms	⊕	13 studies; [16,42,35,36,45,49-55,58,59] *n*=1853	2 studies; [16,54] *n*=203	2 studies; [45,55] *n*=293	NA	4 studies; [35,36,42,49,50] *n*=241	8 studies; [16,35,36,41,42,51-53,59] *n*=1116
- Overall % (95% CI)		33% (22-44%)	9% (4-14%)	NA		33% (14-53%)	36% (27-45%)
- Constipation % (95% CI)		12% (6-17%)	9% (4-14%)	16% (10-23%)		9% (0-19%)	13% (0-35%)
- Diarrhea % (95% CI)		7% (2-12%)	4% (0-7%)	NA		8% (0-20%)	9% (1-17%)
Urogenital symptoms	⊕	4 studies; [16,54,56,57] *n*=247	4 studies; [16,54,56,57] *n*=247	NA	NA	NA	NA
- Impotency % (95% CI)		1% (0-3%)	1% (0-3%)				
- Ejaculation difficulties % (95% CI)		3% (0-7%)	3% (0-7%)				
- Diminished libido % (95% CI)		28% (15-40%)	28% (15-40%)				
- Urinary dysfunction % (95% CI)		9% (4-14%)	9% (4-14%)				

* as percentage of maximum score (10)

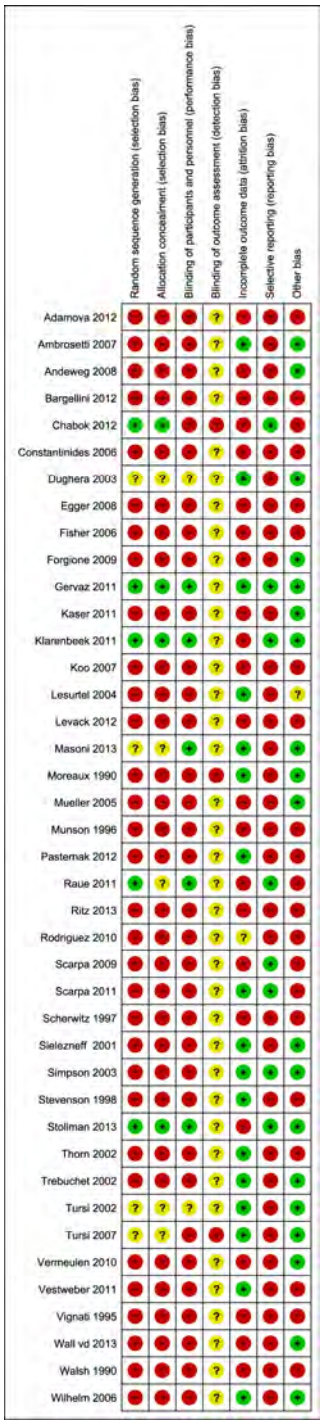


Figure 2: Methodological quality of the studies included in the systematic review

Table 3: Head-to-head comparison of patient-reported outcomes of elective surgical treatment and conservative treatment

Outcome	GRADE	Elective Surgery	*P*
Gastrointestinal related QoL	⊕⊕⊕		
- GICLI score (mean difference ± 95% CI)		+1.0 (-10.6-12.6)	0.87
General QoL	⊕⊕⊕		
- SF-36 (mean difference ± 95% CI)		NA	
- CGQL (mean difference ± 95% CI)*		0.0 (-0.5-0.5)	>0.99
Disability	⊕⊕⊕		
- Prevalence		NA	
Chronic abdominal pain	⊕⊕		
- Prevalence RR (95% CI)		0.96 (0.29-3.17)	0.95
Faecal incontinence	⊕⊕		
- Prevalence		NA	
Satisfaction	⊕⊕		
- Prevalence		NA	
Gastrointestinal symptoms	⊕		
- Overall RR (95% CI)		0.35 (0.16-0.79)	**0.01**
- Constipation RR (95% CI)		0.35 (0.16-0.79)	**0.01**
- Diarrhea RR (95% CI)		0.28 (0.08-1.00)	**0.05**
- Flatulence RR (95% CI)		0.35 (0.16-0.79)	**0.01**
- Painful defecation RR (95% CI)		0.39 (0.17-0.90)	**0.03**
Urogenital symptoms	⊕		
- Prevalence RR (95% CI)		NA	

* as percentage of maximum score (10)
NA: not available
RR: relative risk

Outcomes important for decision-making

The prevalence of chronic abdominal pain (31%, 95% CI: 29-34%) was reported in eight studies evaluating, patients and was not affected by the type of treatment. The prevalence of faecal incontinence (9%, 95% CI: 5-12%) was reported in four studies evaluating 543 patients, and the prevalence of patient satisfaction (96%, 95% CI: 95-98%) was reported in five studies evaluating 344 patients; the type of surgery affected neither outcome. Scores for faecal incontinence and patient satisfaction were not available for the conservative treatments.

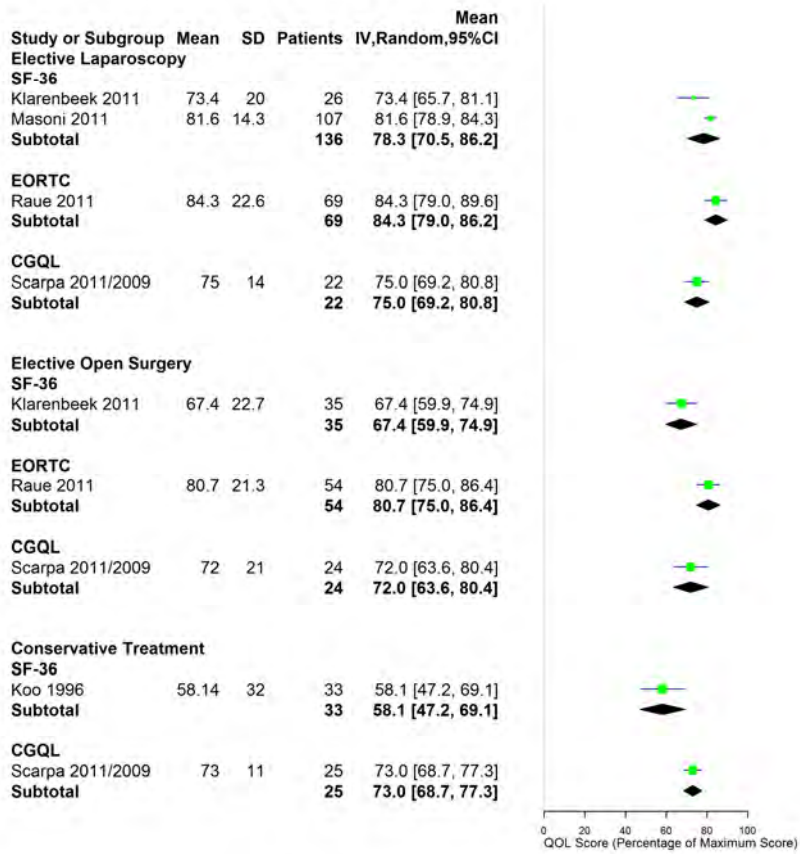


Figure 3: General quality of life (QoL) sorted by type of treatment in patients with diverticulitis

Outcomes of limited importance

The prevalence of persistent gastrointestinal symptoms (28%, 95% CI: 24-31%) was reported in 13 studies evaluating 1,853 patients. Both among cohorts and in a head-to-head analysis, gastrointestinal symptoms were less frequent among patients treated by laparoscopic surgery (prevalence = 9%, 95% CI: 4-14%) than among those who underwent conservative treatment (prevalence = 36%, 95% CI: 27-45%; *Table 3*), although the head-to-head comparison was made in only one study.[16] Heterogeneity among the studies describing persistent symptoms was considerable (I^2 = 91%). Overall gastrointestinal symptoms, flatulence, and painful defecation were all significantly improved among the patients who had undergone surgery (*Figure 4*). Taking into account the head-to-head comparison of elective laparoscopic surgery and conservative treatment, the overall gastrointestinal symptoms, constipation, diarrhea, flatulence, and painful defecation were improved in the laparoscopic group (*Table 3*).

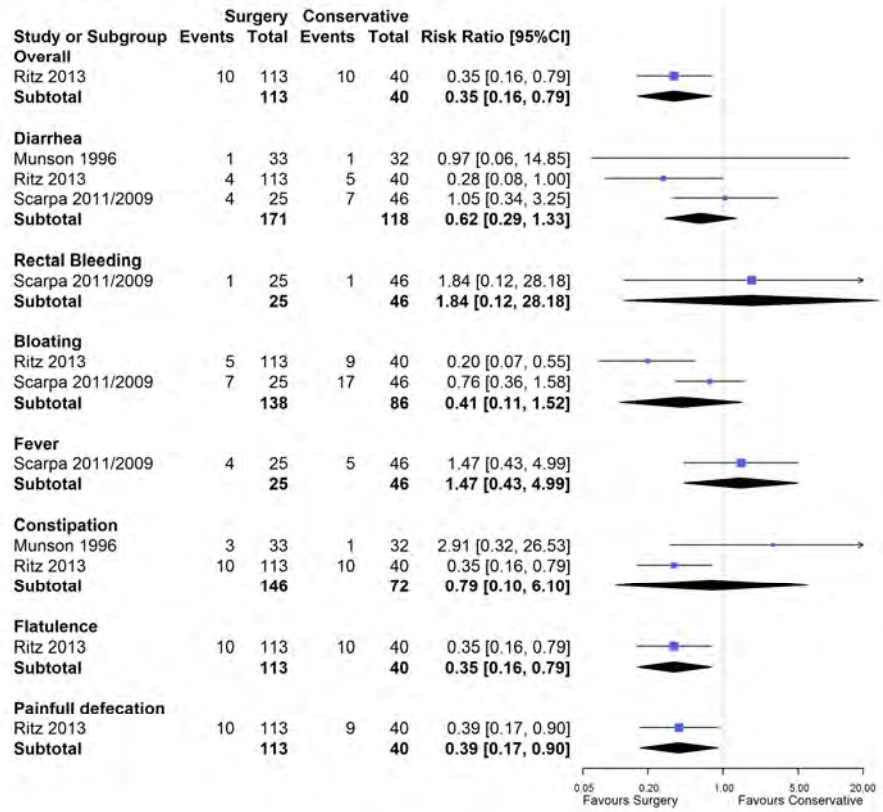


Figure 4: Gastrointestinal symptoms compared between surgical and conservative treatment of diverticulitis

Urogenital symptoms; as measured by prevalence of impotency (1%, 95% CI: 0-3%), ejaculation difficulties (3%, 95% CI: 0-7%), diminished libido (28%, 95% CI: 15-40%), and urinary and sexual dysfunction (9%, 95% CI: 4-14%); were reported in four studies analyzing a total of 247 patients treated with laparoscopic surgery. Scores for urogenital symptoms were not available for the other treatment modalities.

Sensitivity analyses

The sensitivity analyses included the results of the studies that were not eligible for the meta-analysis. None of the sensitivity analyses changed the results for any outcome.

Discussion

Summary of results

We analyzed patient-reported outcomes for surgical and conservative treatments of diverticulitis. None of the included studies had a low risk of bias. The patients reported better general QoL after elective laparoscopic colonic resection compared with conservative treatment, but the difference could not be reproduced in a head-to-head analysis of both treatment options. Gastrointestinal QoL was comparable between the two treatment strategies. Almost one third of the patients reported chronic abdominal pain after surgical or conservative treatment, and the type of treatment did not affect the outcome. Laparoscopic colonic resection resulted in fewer gastrointestinal symptoms compared with conservative treatment, both among cohorts and within one trial directly comparing both treatments. Gastrointestinal symptoms were considered to be of limited importance in clinical decision-making, however.

Strengths and limitations of the study

This is the first systematic review assessing the effects of different treatment modalities on QoL and PROs among patients with diverticulitis. The major strengths of this review are the systematic approach and the use of the GRADE system for ranking outcomes. A large number of studies were included based on an extensive literature search of different databases. The analysis of grey literature and trial registers did not reveal a publication bias. Because of the introduction of minimally invasive surgical techniques, we focused the review on studies published after 1989. The results of the analysis were shown to be robust by extensive sensitivity and subgroup analyses.

All of the selected studies had a high risk of bias, and many of the studies lacked complete follow-up or did not report dropouts correctly. Most of the studies were not randomized, and the staging of primary or recurrent diverticulitis was often poorly described, with considerable heterogeneity among the studies. Many of the surgical cohorts did not differentiate between the results of elective or emergency therapy. Therefore, selection bias within the studies could not be excluded. The exclusion of studies conducted before 1990 may have introduced a bias, although we believe that older studies would not have provided data reflecting the current practice of laparoscopic surgery. Open surgery for complicated diverticulitis was often a three-staged resection prior to 1990, whereas now it is usually a one-staged or two-staged surgery. In addition, conservative treatment with anti-inflammatory agents and intermittent antibiotics has been introduced in recent years.

Comparison with other studies

The optimal treatment strategy for patients with an acute episode of diverticulitis depends on the severity of the disease. In patients with recurrent diverticulitis or persistent abdominal complaints, the need to operate and the timing of the surgery are subjects of debate. Previously, the standard was to perform elective colectomy following

two episodes of diverticulitis to prevent future complicated diverticulitis. Recent data show that recurrent cases are seldom complicated, however, making prophylactic surgery less indicated, especially in light of the risk of morbidity and mortality associated with surgery.[9, 10, 16, 60] Decisions between surgery and conservative treatment need to account for early morbidity and long-term QoL and PROs for the individual patient. Patients may improve QoL and gastrointestinal symptoms by undergoing laparoscopic resection.

For patients presenting with acute diverticulitis, urgent surgery is performed when there are signs of sepsis or diffuse peritonitis or when the condition fails to improve despite medical therapy and/or percutaneous drainage.[8] QoL and PROs are difficult to account for when urgent surgery is needed. Surgical approaches for acute diverticulitis have changed, however, with the intention of causing less morbidity and better QoL with comparable survival. Survivors of perforated diverticulitis have poorer QoL than patients with other forms of diverticulitis, mainly due to the presence of an end colostomy.[28]

The avoidance of Hartmann's procedure by resectional therapy of the affected colonic segment with primary anastomosis and defunctioning loop ileostomy has gained in popularity among patients with Hinchey III/IV diverticulitis.[28, 30, 61] Treatment with laparoscopic lavage and drainage of the abdominal cavity in which the colon is not resected is a promising new approach for patients with purulent peritonitis and may result in better QoL by avoiding an end colostomy, although the results of properly conducted trials are not yet available.[28, 26]

We found a high overall prevalence (almost one in three patients) of chronic abdominal pain after treatment for diverticulitis. A confounding factor might be the co-prevalence of Irritable Bowel Syndrome (IBS) among patients with diverticular disease. A few studies showed an association between IBS and diverticulitis, with overlapping symptoms and pathophysiology.[63-65] Furthermore, an episode of acute diverticulitis can result in post-diverticulitis IBS causing chronic bowel symptoms, possibly due to changes in the colon wall.[65] Because the symptoms of diverticulitis can mimic those of inflammatory bowel disease, patients (especially those who are elderly) are often misdiagnosed as having diverticulitis. The treatments for diverticulitis and inflammatory bowel disease are not similar, and bowel symptoms in misdiagnosed patients may persist despite intervention.[66]

Implications for clinical practice

We have shown that elective laparoscopic colonic resection may be better than conservative treatment in terms of improving the QoL and gastrointestinal symptoms of patients with diverticulitis. The quality and power of the studies supporting this finding are low, however. Therefore, a re-evaluation of the most important determinants of treatment success following laparoscopic surgery and conservative treatment reported by patients with recurrent episodes of diverticulitis is justified. Especially for young patients with low comorbidity for whom bowel symptoms might have strong social implications,

elective surgery could be a valuable treatment option. Our findings also indicate that clinical practice should move away from one-size-fits-all guidelines on when to operate towards a more individualized approach, assessing the operative risk and the potential gain in QoL for the individual patient.

Conclusions

The available evidence on QoL among patients treated for diverticulitis is limited, and heterogeneity among the existing studies is substantial. There is a benefit favoring elective laparoscopy, however, for recurrent diverticulitis in terms of general QoL and gastro-intestinal symptoms. Further high-quality trials focusing on patient-reported outcomes and QoL are needed.

Reference list

1 Lidsky ME, Thacker JK, Lagoo-Deenadayalan SA, and Scarborough JE. Advanced age is an independent predictor for increased morbidity and mortality after emergent surgery for diverticulitis. Surgery. 2012, Sep;152(3):465-72.

2 Delvaux M. Diverticular disease of the colon in Europe: epidemiology, impact on citizen health and prevention. Aliment Pharmacol Ther. 2003, Nov;18 Suppl 371-4.

3 Szojda MM, Cuesta MA, Mulder CM, and Felt-Bersma RJ. Review article: Management of diverticulitis. Aliment Pharmacol Ther. 2007, Dec;26 Suppl 267-76.

4 Schoetz DJ. Diverticular disease of the colon: a century-old problem. Dis Colon Rectum. 1999, Jun;42(6):703-9.

5 Andeweg CS, Mulder IM, Felt-Bersma RJ, Verbon A, van der Wilt GJ, van Goor H, et al. Guidelines of Diagnostics and Treatment of Acute Left-Sided Colonic Diverticulitis. Dig Surg. 2013, Aug 20;30(4-6):278-292.

6 Morris CR, Harvey IM, Stebbings WS, and Hart AR. Incidence of perforated diverticulitis and risk factors for death in a UK population. Br J Surg. 2008, Jul;95(7):876-81.

7 Ricciardi R, Baxter NN, Read TE, Marcello PW, Hall J, and Roberts PL. Is the decline in the surgical treatment for diverticulitis associated with an increase in complicated diverticulitis? Dis Colon Rectum. 2009, Sep;52(9):1558-63.

8 Rafferty J, Shellito P, Hyman NH, Buie WD, and Standards Committee of American Society of Colon and Rectal Surgeons. Practice parameters for sigmoid diverticulitis. Dis Colon Rectum. 2006, Jul;49(7):939-44.

9 Broderick-Villa G, Burchette RJ, Collins JC, Abbas MA, and Haigh PI. Hospitalization for acute diverticulitis does not mandate routine elective colectomy. Arch Surg. 2005, Jun;140(6):576-81; discussion 581-3.

10 Chapman JR, Dozois EJ, Wolff BG, Gullerud RE, and Larson DR. Diverticulitis: a progressive disease? Do multiple recurrences predict less favorable outcomes? Ann Surg. 2006, Jun;243(6):876-830; discussion 880-3.

11 Regenbogen SE, Hardiman KM, Hendren S, and Morris AM. Surgery for Diverticulitis in the 21st Century: A Systematic Review. JAMA Surg. 2014, Jan 15;

12 Peppas G, Bliziotis IA, Oikonomaki D, and Falagas ME. Outcomes after medical and surgical treatment of diverticulitis: a systematic review of the available evidence. J Gastroenterol Hepatol. 2007, Sep;22(9):1360-8.

13 Moreno AM, and Wille-Jørgensen P. Long-term outcome in 445 patients after diagnosis of diverticular disease. Colorectal Dis. 2007, Jun;9(5):464-8.

14 Simpson J, Neal KR, Scholefield JH, and Spiller RC. Patterns of pain in diverticular disease and the influence of acute diverticulitis. Eur J Gastroenterol Hepatol. 2003, Sep;15(9):1005-10.

15 Klarenbeek BR, Veenhof AA, Bergamaschi R, van der Peet DL, van den Broek WT, de Lange ES, et al. Laparoscopic sigmoid resection for diverticulitis decreases major morbidity rates: a randomized control trial: short-term results of the Sigma Trial. Ann Surg. 2009, Jan;249(1):39-44.

16 Ritz JP, Gröne J, Engelmann S, Lehmann KS, Buhr HJ, and Holmer C. [What is the actual benefit of sigmoid resection for acute diverticulitis? : Functional outcome after surgical and conservative treatment]. Chirurg. 2013, Aug;84(8):673-80.

17 Forgione A, Leroy J, Cahill RA, Bailey C, Simone M, Mutter D, and Marescaux J. Prospective evaluation of functional outcome after laparoscopic sigmoid colectomy. Ann Surg. 2009, Feb;249(2):218-24.
18 Pasternak I, Wiedemann N, Basilicata G, and Melcher GA. Gastrointestinal quality of life after laparoscopic-assisted sigmoidectomy for diverticular disease. Int J Colorectal Dis. 2012, Jun;27(6):781-7.
19 Morris AM, Regenbogen SE, Hardiman KM, and Hendren S. Sigmoid diverticulitis: a systematic review. JAMA. 2014, Jan 15;311(3):287-97.
20 Carr AJ, and Higginson IJ. Are quality of life measures patient centred? BMJ. 2001, Jun 2;322(7298):1357-60.
21 Basch E. New Frontiers in Patient-Reported Outcomes: Adverse Event Reporting, Comparative Effectiveness, and Quality Assessment. Annu Rev Med. 2013, Nov 20;
22 Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ, and GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008, May 3;336(7651):995-8.
23 Acosta JA, Grebenc ML, Doberneck RC, McCarthy JD, and Fry DE. Colonic diverticular disease in patients 40 years old or younger. Am Surg. 1992, Oct;58(10):605-7.
24 Stollman N, Magowan S, Shanahan F, Quigley EM, and DIVA Investigator Group. A randomized controlled study of mesalamine after acute diverticulitis: results of the DIVA trial. J Clin Gastroenterol. 2013, Aug;47(7):621-9.
25 Van de Wall BJ, Draaisma WA, van Iersel JJ, Consten EC, Wiezer MJ, and Broeders IA. Elective resection for ongoing diverticular disease significantly improves quality of life. Dig Surg. 2013;30(3):190-7.
26 Gervaz P, Mugnier-Konrad B, Morel P, Huber O, and Inan I. Laparoscopic versus open sigmoid resection for diverticulitis: long-term results of a prospective, randomized trial. Surg Endosc. 2011, Oct;25(10):3373-8.
27 Rodríguez-Cerrillo M, Poza-Montoro A, Fernandez-Diaz E, and Romero AI. Patients with uncomplicated diverticulitis and comorbidity can be treated at home. Eur J Intern Med. 2010, Dec;21(6):553-4.
28 Vermeulen J, and Lange JF. Treatment of perforated diverticulitis with generalized peritonitis: past, present, and future. World J Surg. 2010, Mar;34(3):587-93.
29 Adamova, Z., Comparison of long-term quality of life in patients with diverticular disease. Are there any benefits to surgery? Central European Journal of Medicine; Cent Eur J Med, 2012(5): p. 571-577.
30 Constantinides VA, Aydin HN, Tekkis PP, Fazio VW, Heriot AG, and Remzi FH. Long-term, health-related, quality of life comparison in patients undergoing single stage vs staged resection for complicated diverticular disease. Colorectal Dis. 2006, Oct;8(8):663-71.
31 Klarenbeek BR, Samuels M, van der Wal MA, van der Peet DL, Meijerink WJ, and Cuesta MA. Indications for elective sigmoid resection in diverticular disease. Ann Surg. 2010, Apr;251(4):670-4.
32 Koo V, Strange J, Lam CY, and Epanomeritakis M. Young patients with diverticular disease: a preliminary quality of life study. Int J Surg. 2007, Aug;5(4):244-9.
33 Masoni L, Mari FS, Nigri G, Favi F, Gasparrini M, Dall'Oglio A, et al. Preservation of the inferior mesenteric artery via laparoscopic sigmoid colectomy performed for diverticular disease: real benefit or technical challenge: a randomized controlled clinical trial. Surg Endosc. 2013, Jan;27(1):199-206.

34 Raue W, Paolucci V, Asperger W, Albrecht R, Büchler MW, Schwenk W, and LAPDIV-CAMIC Trial Group. Laparoscopic sigmoid resection for diverticular disease has no advantages over open approach: midterm results of a randomized controlled trial. Langenbecks Arch Surg. 2011, Oct;396(7):973-80.

35 Scarpa M, Pagano D, Ruffolo C, Pozza A, Polese L, Frego M, et al. Health-related quality of life after colonic resection for diverticular disease: long-term results. J Gastrointest Surg. 2009, Jan;13(1):105-12.

36 Scarpa M, Griggio L, Rampado S, Ruffolo C, Citton M, Pozza A, et al. Long-term health-related quality of life after minimally invasive surgery for diverticular disease. Langenbecks Arch Surg. 2011, Aug;396(6):833-43.

37 Vestweber B, Straub E, Kaldowski B, Paul C, Alfes A, Haaf F, and Vestweber KH. [Single-port colonic surgery : techniques and indications]. Chirurg. 2011, May;82(5):411-4, 416-8.

38 Andeweg C, Peters J, Bleichrodt R, and van Goor H. Incidence and risk factors of recurrence after surgery for pathology-proven diverticular disease. World J Surg. 2008, Jul;32(7):1501-6.

39 Bargellini T, Martellucci J, Tonelli P, and Valeri A. Long-term results of treatment of acute diverticulitis: still lessons to be learned? Updates Surg. 2012, Dec 28;

40 Chabok A, Påhlman L, Hjern F, Haapaniemi S, Smedh K, and AVOD Study Group. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg. 2012, Apr;99(4):532-9.

41 Mueller MH, Glatzle J, Kasparek MS, Becker HD, Jehle EC, Zittel TT, and Kreis ME. Long-term outcome of conservative treatment in patients with diverticulitis of the sigmoid colon. Eur J Gastroenterol Hepatol. 2005, Jun;17(6):649-54.

42 Munson KD, Hensien MA, Jacob LN, Robinson AM, and Liston WA. Diverticulitis. A comprehensive follow-up. Dis Colon Rectum. 1996, Mar;39(3):318-22.

43 Wilhelm TJ, Refeidi A, Palma P, Neufang T, and Post S. Hand-assisted laparoscopic sigmoid resection for diverticular disease: 100 consecutive cases. Surg Endosc. 2006, Mar;20(3):477-81.

44 Levack MM, Savitt LR, Berger DL, Shellito PC, Hodin RA, Rattner DW, et al. Sigmoidectomy syndrome? Patients' perspectives on the functional outcomes following surgery for diverticulitis. Dis Colon Rectum. 2012, Jan;55(1):10-7.

45 Sielezneff I, Malouf AJ, Pirro N, Cesari J, Brunet C, and Sastre B. Short-term functional outcome following elective surgery for complicated sigmoid diverticular disease: sutured or stapled end-to-end anastomosis to the proximal rectum? Colorectal Dis. 2001, Jan;3(1):23-7.

46 Ambrosetti P, Francis K, Weintraub D, and Weintraub J. Functional results following elective laparoscopic sigmoidectomy after CT-proven diagnosis of acute diverticulitis evaluation of 43 patients and review of the literature. J Gastrointest Surg. 2007, Jun;11(6):767-72.

47 Thörn M, Graf W, Stefànsson T, and Påhlman L. Clinical and functional results after elective colonic resection in 75 consecutive patients with diverticular disease. Am J Surg. 2002, Jan;183(1):7-11.

48 Walsh RM, Aranha GV, and Freeark RJ. Mortality and quality of life after total abdominal colectomy. Arch Surg. 1990, Dec;125(12):1564-6.

49 Egger B, Peter MK, and Candinas D. Persistent symptoms after elective sigmoid

resection for diverticulitis. Dis Colon Rectum. 2008, Jul;51(7):1044-8.

50 Scherwitz P, Mönig SP, Schmitz-Rixen T, and Raab M. [Long-term results of abdominal surgery interventions. Different evaluation from the viewpoint of the patient, the surgeon and the public health office]. Langenbecks Arch Chir. 1997;382(1):19-24.

51 Tursi A, Brandimarte G, and Daffinà R. Long-term treatment with mesalazine and rifaximin versus rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon. Dig Liver Dis. 2002, Jul;34(7):510-5.

52 Tursi A. New physiopathological and therapeutic approaches to diverticular disease of the colon. Expert Opin Pharmacother. 2007, Feb;8(3):299-307.

53 Vignati PV, Welch JP, and Cohen JL. Long-term management of diverticulitis in young patients. Dis Colon Rectum. 1995, Jun;38(6):627-9.

54 Stevenson AR, Stitz RW, Lumley JW, and Fielding GA. Laparoscopically assisted anterior resection for diverticular disease: follow-up of 100 consecutive patients. Ann Surg. 1998, Mar;227(3):335-42.

55 Moreaux J, and Vons C. Elective resection for diverticular disease of the sigmoid colon. Br J Surg. 1990, Sep;77(9):1036-8.

56 Trebuchet G, Lechaux D, and Lecalve JL. Laparoscopic left colon resection for diverticular disease. Surg Endosc. 2002, Jan;16(1):18-21.

57 Lesurtel M, Fritsch S, Sellam R, Molinier N, and Mosnier H. Does laparoscopic colorectal resection for diverticular disease impair male urinary and sexual function? Surg Endosc. 2004, Dec;18(12):1774-7.

58 Käser SA, Glauser PM, Basilicata G, Müller DA, and Maurer CA. Timing of rectosigmoid resection for diverticular disease: the patient's view. Colorectal Dis. 2012, Mar;14(3):e111-6.

59 Fischer, F., et al., Quality of life and functional outcome after conventional and laparoscopic surgery for diverticulitis (Hinchey I and II). Viszeralchirurgie; Viszeralchirurgie, 2006(5): p. 347-353.

60 Eglinton T, Nguyen T, Raniga S, Dixon L, Dobbs B, and Frizelle FA. Patterns of recurrence in patients with acute diverticulitis. Br J Surg. 2010, Jun;97(6):952-7.

61 Salem L, Veenstra DL, Sullivan SD, and Flum DR. The timing of elective colectomy in diverticulitis: a decision analysis. J Am Coll Surg. 2004, Dec;199(6):904-12.

62 Swank HA, Vermeulen J, Lange JF, Mulder IM, van der Hoeven JA, Stassen LP, et al. The ladies trial: laparoscopic peritoneal lavage or resection for purulent peritonitisA and Hartmann's procedure or resection with primary anastomosis for purulent or faecal peritonitisB in perforated diverticulitis (NTR2037). BMC Surg. 2010;1029.

63 Spiller R. Is it diverticular disease or is it irritable bowel syndrome? Dig Dis. 2012;30(1):64-9.

64 Strate LL, Modi R, Cohen E, and Spiegel BM. Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights. Am J Gastroenterol. 2012, Oct;107(10):1486-93.

65 Cohen E, Fuller G, Bolus R, Modi R, Vu M, Shahedi K, et al. Increased risk for irritable bowel syndrome after acute diverticulitis. Clin Gastroenterol Hepatol. 2013, Dec;11(12):1614-9.

66 Gurudu S, Fiocchi C, and Katz JA. Inflammatory bowel disease. Best Pract Res Clin Gastroenterol. 2002, Feb;16(1):77-90.

Table S1: Characteristics of included studies evaluating patients with diverticulitis

Reference	Design	Patients	Intervention	*N*	*N* after follow-up	Outcomes	Follow-up		Results
							preoperative	postoperative	
Open versus laparoscopic elective surgery									
Klarenbeek (2011)[31]	RCT	Recurrent Hinchey I, IIa, IIb diverticulitis Surgery at least 3 months after last episode	Laparoscopic or open surgery	52 (laparoscopic) 52 (open)	29 (laparoscopic) 35 (open)	SF-36[a]	Yes	6 weeks and 6 months	QoL after 6 months showed no significant difference between the two groups After six weeks laparascopic surgery was preferred
Fischer (2006)[59]	Cohort	Hinchey I, IIa Diverticulitis, not further specified	Laparoscopic or open surgery	125 (laparoscopic) 267 (open)	45 (laparoscopic) 45 (open)	SF-36[a] Faecal incontinence (CACP score)[b] Bowel symptoms (Wexner score)[c]	No	Mean 6 years (laparoscopic) Mean 9 years (open)	QoL, faecal incontinence and constipation showed no significant difference between the two groups
Gervaz (2011)[26]	RCT	Recurrent Hinchey I,II, not further specified	Laparoscopic or open surgery	59 (laparoscopic) 51 (open)	54 (laparoscopic) 51 (open)	GIQLI[d] Satisfaction (measured on a scale from 0 (very unhappy) to 10 (completely satisfied)	No	Median 30 months (laparoscopic) Median 29 months (open)	Median GIQLI score was 115 in open surgery group compared to 110 in laparoscopic group (p=0.17) Overall satisfaction was 9 in open surgery group versus 9 in laparoscopic group (p=0.78)
Raue (2011)[34]	RCT	Hansen and Stock II/III Proven by CT or US and colonoscopy Surgery at least 14 days after last episode	Laparoscopic or open surgery	77 (laparoscopic) 79 (open)	69 (laparoscopic) 54 (open)	EORTC-QLQ-C30[e]	Yes	7 days, 30 days, 3 months and 12 months	QoL was not significantly different between the two groups after 7, 30, 90 days and 12 months after surgery. Operation time was longer in de laparoscopic group

Table S1: Characteristics of included studies evaluating patients with diverticulitis

Reference	Design	Patients	Intervention	*N*	*N* after follow-up	Outcomes	Follow-up		Results
							preoperative	postoperative	
Laparoscopic elective surgery									
Forgione (2009)[17]	Cohort	Patients with at least 1 episode of diverticulitis Proven by CT Mean time between 1st episode and surgery 3.4 years	Laparoscopic surgery	48	40	GIQLI[d] Urinary function (IPSS[i], UDI[g]) Sexual function (IEEF-5)[h]	Yes	3, 6 and 12 months	Postoperative GIQLI scores were significantly higher at every time point. Those with the lowest scores preoperatively gained the most postoperatively Urinary and sexual dysfunction didn't show significant difference pre- and postoperatively
Pasternak (2012)[18]	Cohort	Recurrent diverticulitis Proven by endoscopy or CT Surgery about 6 weeks after last episode	Laparoscopic surgery	130	120	GIQLI[d] Satisfaction (% of satisfied patients)	Yes	Mean 40 months	Elective laparoscopic sigmoid resection shows a significant increase in disease specific QoL 96% regarded the operation as successful
Ambrosetti (2007)[46]	Cohort	Patients with at least 1 episode of diverticulitis Proven by CT Surgery about 110 days after last episode	Laparoscopic surgery	45	43	Bowel symptoms, not further specified Satisfaction (degree of satisfaction, % of patients)	Yes	Mean 40 months	Bowel function was considered better in 56%, unchanged in 37% and worse in 7% Final result was reported to be excellent to good in 47%, satisfying in 40% and mediocre in 13%
Stevenson (1998)[54]	Cohort	Patients >55 years of age with at least 2 episodes of diverticulitis or complicated diverticular disease or <55 years and 1 episode	Laparoscopic surgery	100	90	Bowel symptoms (% of patients symptom free, improvement of symptoms, frequency bowel habit) Sexual function, not further specified	No	Median 37 months	93% reported improvement of their bowel symptoms 80% was symptom free after surgery Bowel habit was more regular in 68%, while 20% remained unchanged Retrograde ejaculation was reported by 1/37 men (3%)

Table S1: Characteristics of included studies evaluating patients with diverticulitis

Reference	Design	Patients	Intervention	*N*	*N* after follow-up	Outcomes	Follow-up		Results
							preoperative	postoperative	
Lesurtel (2004)[57]	Cohort	Symptomatic diverticular disease, not further specified Only male patients	Laparoscopic surgery	53	51	Urinary function (IPSS[f], UFSS[i]) Sexual function (% of patients with sexual dysfunction)	No	Mean 27 months	Urinary and sexual dysfunction didn't show significant difference pre- and postoperatively
Trebuchet (2002)[56]	Cohort	Symptomatic diverticular disease (one or more attacks of diverticulitis, abscess, stenosis, fistula) Sexual function was only reported in men	Laparoscopy	92	92	Sexual function (% of patients with sexual impotency or retrograde ejaculation)	Yes	Mean 42 months	1% reported sexual impotency and 8% reported retrograde ejaculation
Vestweber (2011)[37]	Cohort	Diverticulitis of the sigmoid, not further specified Surgery about 3.92 weeks after last episode	Laparoscopy	120	120	Disability (complaints during exercise)	No	Mean 7.5 months	Overall disability of 6%
Wilhelm (2006)[43]	Cohort	Recurrent or acute diverticulitis, stenosis, bleeding, fistula Surgery at least 4 weeks after last episode (recurrent) ór <7 days (acute diverticulitis)	Laparoscopy	100	90	Pain (% of patients with slight or severe abdominal pain) Satisfaction (% of patients satisfied)	No	Mean 19 months	97% of the patients are satisfied 21% of the patients reported slight abdominal pain and 2% severe
Masoni (2013)[33]	RCT	Symptomatic diverticular disease, not further specified	Laparoscopy (IMAP)[r] Laparoscopy (IMAS)[s]	69 (IMAP) 64 (IMAS)	54 (IMAP) 53 (IMAS)	SF-36[a] Faecal incontinence (IS)[j] Bowel symptoms (Wexner score)[c]	No	6 months	QoI, using the SF-36, was significantly greater in the IMAP group when considering physical function, physical role, general health, social functioning, emotional role The frequency of gas incontinence, the need of wearing a pad and constipation symptoms were significantly lower in the IMAP group

Table S1: Characteristics of included studies evaluating patients with diverticulitis

Reference	Design	Patients	Intervention	*N*	*N* after follow-up	Outcomes	Follow-up		Results
							preoperative	postoperative	
Open elective surgery									
Sielezneff (2001)[45]	Cohort	Complicated diverticular disease (stricture, recurrent diverticulitis, prior abscess, fistula, anaemia)	Open surgery (hand-sewn vs stapled anastomosis)	67 (hand-sewn) 49 (stapled)	67 (hand-sewn) 49 (stapled)	Faecal incontinence (% of patients with incontinence to solid and liquid stool or flatus) Bowel symptoms (% of patients with constipation, dyschesia, consistency and frequency of stool, and use of laxatives)	Yes	6 months	3.5% of patients developed postoperative faecal incontinence, no significant difference between the two groups Constipation (p=0.005) and dyschesia (p=0.03) were significantly more common in stapled group
Moreaux (1990)[55]	Cohort	Symptomatic diverticular disease (Fistula, >2 episodes of diverticulitis, chronic symptoms, obstruction)	Open surgery	177	177	Bowel symptoms (% of patients with persistent pain, intestinal dysfunction)	No	Mean 5.8 years	85% of the patients are symptom free, 11% report persistent pain or intestinal dysfunction and 3% report recurrent attacks of pain or fever after surgery
Thorn (2002)[47]	Cohort	Symptomatic diverticular disease (one or more episodes of diverticulitis, stenosis, abscess, functional problems)	Open surgery	75	64	Bowel symptoms (questionnaire bowel function: i.e. stool characteristics, constipation, bowel movements/week)	Yes	Mean 4.0 years	78% of the patients report excellent to good bowel function, 20% fair and 2% worse after surgery
Emergency surgery for complicated diverticulitis									
Vermeulen (2010)	Cohort	Complicated diverticulitis (acute perforated diverticulitis, Hinchey III,IV)	Hartmann's procedure (HP) and primary anastomosis (PA)	139 (HP) 61 (PA)	76 (HP) 53 (PA)	EORTC-QLQ-C30[c]	No	Median 71 months	PA patients had significantly higher scores with regard to global health status, physical function, fatique, dyspnea and body image

Table S1: Characteristics of included studies evaluating patients with diverticulitis

Reference	Design	Patients	Intervention	*N*	*N* after follow-up	Outcomes	Follow-up		Results
							preoperative	postoperative	
Emergency and elective surgery									
Constanti-nides (2006)[30]	Cohort	Complicated diverticular disease (phlegmon, abscess, perforation, obstruction, fistula, bleeding, stricture, Hinchey 0-IV)	Hartmann (HP) and primary anastomosis (PA)	230 (HP and PA, data not specified per surgery category)	158 (HP) 30 (PA)	SF-36[a] Faecal incontinence (% of patients wearing pad during day/night)	No	Median 5 years	QoL showed no significant difference between the two groups Postoperative complications significantly reduced QoL scores for three domains When considering the use of pads no significant difference was observed between the two groups
Levack (2012)[44]	Cohort	Diverticulitis	Laparoscopic or open surgery No comparison	325	249	Faecal incontinence (FISI[k], MBFI[l])	No	Median 50.1 months	Moderate to severe faecal incontinence: 24.8% (FISI score> 24) Faecal urgency: 19.6% (MBFI-Urgency Subscale ≥4) Incomplete emptying: 20.8% (MBFI-Emptying Subscale ≥4)[c]
Andeweg (2008)[38]	Cohort	Complicated and uncomplicated diverticulitis Proven by pathology	Elective and emergency surgery	183 (data not specified per surgery category)	110 (elective surgery) 73 (emergency surgery)	Pain (% of patients with postoperative pain)	No	Mean 7.2 years	Persistent postoperative pain 22.1%
Egger (2008)[49]	Cohort	Complicated and uncomplicated diverticulitis (Hinchey 1a-V) Proven by CT	Elective and emergency surgery	162 (data not specified per surgery category)	68 (elective surgery) 56 (emergency surgery)	Disability Bowel symptoms (% of patients with constipation, abdominal distension, cramps, diarrhea)	No	Mean 33 months	Persistent symptoms after elective surgery 25% and after emergency surgery 23% Resume to work after elective laparoscopic surgery 5.7 weeks, and after open surgery 5.9 weeks
Kaser (2012)[58]	Cohort	Recurrent (two or more episodes of diverticulitis) Hinchey 0-III	Laparoscopic and open surgery No comparison	236 (data not specified per surgery category)	117	Bowel symptoms (degree of improvement of symptoms, % of patients)	Yes	>3 months	Complaints resolved: 54% Marked improvement: 34% Some improvement: 10% No improvement: 2% 38% of patients would have preferred an earlier resection

Table S1: Characteristics of included studies evaluating patients with diverticulitis

Reference	Design	Patients	Intervention	*N*	*N* after follow-up	Outcomes	Follow-up		Results
							preoperative	postoperative	
Scherwitz (1996)[50]	Cohort	Diverticulitis, not further specified	NR	71	59	Bowel symptoms (% of patients symptom free)	No	Median 5 years	55.9 % of patients were symptom free
Walsh (1990)[48]	Cohort	Diverticulitis, not further specified	Total abdominal colectomy	30	27	Satisfaction (degree of satisfaction, % of patients)	No	Mean 4.5 years	Patient satisfaction was excellent: 41%, good: 30%, fair: 18% and poor in 11% of the patients
Van de Wall (2013)[25]	Cohort	Patients with at least 1 episode of diverticulitis Proven by radiology Surgery 7 (3-55) months after primary episode	Laparoscopic and open surgery	137 (data not specified per surgery category	97 (laparoscopic) 8 (open)	Pain (VAS^m score) Bowel symptoms (VAS^m score for abnormal defaecation)	No	Median 33 months	The VAS score for abdominal pain decreased from 80 to 20 after surgery Elective resection improved abdominal pain in 87.5% of patients The VAS score for abnormal defaecation decreased from 63 to 30 after surgery Elective resection improved defaecation in 77.1%
Conservative and surgical treatment									
Bargellini (2012)[39]	Cohort	Diverticulitis Hinchey 0-IV Elective resection 30-90 days after last episode	Medical treatment and elective laparoscopic surgery and emergency laparoscopic or open surgery	202 (data not specified per type of treatment)	52 (medical) 36 (elective laparoscopic) 58 (emergency laparoscopic or open surgery	$CGQL^n$ Pain (% of patients with persistent abdominal pain)	No	Median 99 months	Total CGQL score showed no significant difference between the three groups Persistent pain after medical therapy 11.5%, after surgical therapy 12. 7% (p=0.236)

Table S1: Characteristics of included studies evaluating patients with diverticulitis

Reference	Design	Patients	Intervention	*N*	*N* after follow-up	Outcomes	Follow-up		Results
							preoperative	postoperative	
Adamova (2012)[29]	Cohort	Diverticulitis Hinchey I-II Proven by CT or ultrasound	Medical treatment and elective open surgery and emergency open surgery	123 (data not specified per type of treatment)	50 (medical) 18 (elective open surgery) 9 (emergency open surgery)	GIQLI[d]	No	Mean 7 years	GIQLI score showed no significant difference between surgery (109) and medical therapy (107)
Ritz (2013)[16]	Cohort	Diverticulitis, Hansen and Stock I, IIa, IIb Proven by CT	Medical treatment and laparoscopic surgery	40 (medical) 153 (laparoscopic surgery)	40 (medical) 113 (laparoscopic surgery)	Faecal incontinence (% of patients with faecal incontinence) Bowel symptoms (% of patients with painful defecation, obstipation, diarrhea, bloating, cramps) Sexual function (% of patients with painful sexual intercourse, erectile dysfunction, retrograde ejaculation) Urinary function (% of patients with bladder emptying disorders or stress incontinence)	No	Median 32 months	Postoperative faecal incontinence: 11% % of persistent symptoms was significantly lower in the surgery group (8.8%), compared to the medical group (25%) (p=0.009) Postoperative sexual dysfunction: 7% Postoperative urinary dysfunction: 9%
Munson (1996)[42]	Cohort	Diverticulitis, not further specified Proven by radiology or histology	Medical treatment and surgical treatment	78 (data not specified per type of treatment)	32 (medical) 33 (surgery)	Faecal incontinence (% of patients with faecal incontinence) Pain (% of patients with occasional or frequent pain)	No	1.9 years Median or mean not reported	Postoperative faecal incontinence: 3% Persistent pain after medical therapy 62.5%, after surgery 27.2%

Table S1: Characteristics of included studies evaluating patients with diverticulitis

Reference	Design	Patients	Intervention	*N*	*N* after follow-up	Outcomes	Follow-up		Results
							preoperative	postoperative	
Koo (2007)[32]	Cohort	Diverticulitis <50 yr Proven by radiology or histopathology	Medical treatment and surgical treatment	41 (medical) 6 (surgical treatment)	33 (medical) 5 (surgical treatment)	SF-36[a]	No	Mean 11.4 months (medical) Mean 8.4 months (surgical)	QoL showed no significant difference between the two groups
Scarpa (2011)[36]	Cohort	Diverticulitis Hinchey 0-IV Proven by radiology	Medical treatment and laparoscopic and open surgery	NR	25 (medical) 22 (laparoscopic) 24 (open surgery)	CGQL[n] Bowel symptoms (DDSS[o], BSFS[p])	No	Median 48 months (medical) Median 64 months (laparoscopic) Median 42 months (open surgery)	CGQL score showed no significant difference between the three groups DDSS and BSFS scores showed no significant difference between the three groups
Scarpa (2009)[35]	Cohort	Diverticulitis Hinchey 0-IV Proven by radiology	Medical and surgical treatment (Laparoscopy and open surgery)	149 (not further specified by type of treatment)	46 (medical) 25 (surgery)	CGQL[n] Pain (% of patients with persistent pain) Bowel symptoms (% of patients with fever, constipation, diarrhea, bleeding bloating)	No	Median 47 months	CGQL total scores showed no significant difference between the two groups Persistent pain after medical therapy 43%, after surgery 43% (p=1.000) % of bowel symptoms showed no significant difference between the two groups
Reference	**Design**	**Patients**	**Intervention**	***N***	***N* after follow-up**	**Outcomes**	**Follow-up**		**Results**
							before treatment	**after treatment**	
Conservative treatment									
Chabok (2012)[40]	RCT	Acute uncomplicated left diverticulitis Proven by CT	Intravenous (IV) fluids or antibiotic treatment (AB) for at least 7 days	309 (IV fluids) 314 (AB)	290 (IV fluids) 292 (AB)	Pain (% of patients with persistent pain) Bowel symptoms (% of patients with change of stool)	No	12 months	Persistent mild to chronic pain after treatment without antibiotics: 46%, with antibiotics: 46% Bowel habits showed no significant difference between the two groups

Table S1: Characteristics of included studies evaluating patients with diverticulitis

Reference	Design	Patients	Intervention	*N*	*N* after follow-up	Outcomes	Follow-up		Results
							before treatment	after treatment	
Tursi (2007)[52]	RCT	At least 1 attacks of uncomplicated diverticulitis Proven by colonoscopy and laboratory findings	Balsalazide and probiotic or probiotic treatment alone for 12 months	15 (Balsalazide and probiotic) 15 (probiotic)	14 (Balsalazide and probiotic) 14 (probiotic)	Bowel symptoms (% of patients with constipation, diarrhea, pain, bloating, tenesmus, bleeding, mucus with stools)	No	10 days and 1 month, 2 months, 6 months and 12 months	Persistent mild symptoms were not significantly different between the two groups (13 vs. 13%)
Stollmann (2013)[24]	RCT	Uncomplicated diverticulitis Proven by CT	Mesalamine or Mesalamine and probiotic treatment or placebo for 3 months	40 (Mesalamine) 36 (Mesalamine and probiotic) 41 (placebo)	27 (Mesalamine) 24 (Mesalamine and probiotic) 22 (probiotic)	Bowel symptoms (GSS)[q]	Yes	10 days and 6 weeks,12 weeks , 26 weeks, 39 weeks and 52 weeks	GSS decreased in all groups during the study, though no significant difference could be found
Tursi (2002)[51]	RCT	At least 2 attacks of uncomplicated diverticulitis last year Proven by colonoscopy or x-ray	Rifaximin or Mesalazine (7 days, followed by 7 days/month) Rifaximin treatment for (7 days, followed by 7 days/month)	109 (Mesalazine and Rifaximin) 109 (Rifaximin)	104 (Mesalazine and Rifaximin) 89 (Rifaximin)	Bowel symptoms (quantitative scale for intensity of symptoms and bowel habits)	Yes	3 months, 6 months, 9 months and 12 months	After 12 months percentage of symptom free patients showed significant difference: Mesalazine/Rifaximin 86%, Rifaximin only 49% (p=0.0005) Regular bowel habits with Mesalazine/Rifaximin 79%, Rifaximin only 60% (p=0.001)
Mueller (2005)[41]	Cohort	Uncomplicated diverticulitis Proven by radiology	Conservative treatment	363	85	Pain (% of patients with persistent pain) Bowel symptoms (% of patients with recurrence of symptoms)	No	Median 89 months and 160 months	After 160 months Abdominal pain: 32% Recurrence symptoms: 37%

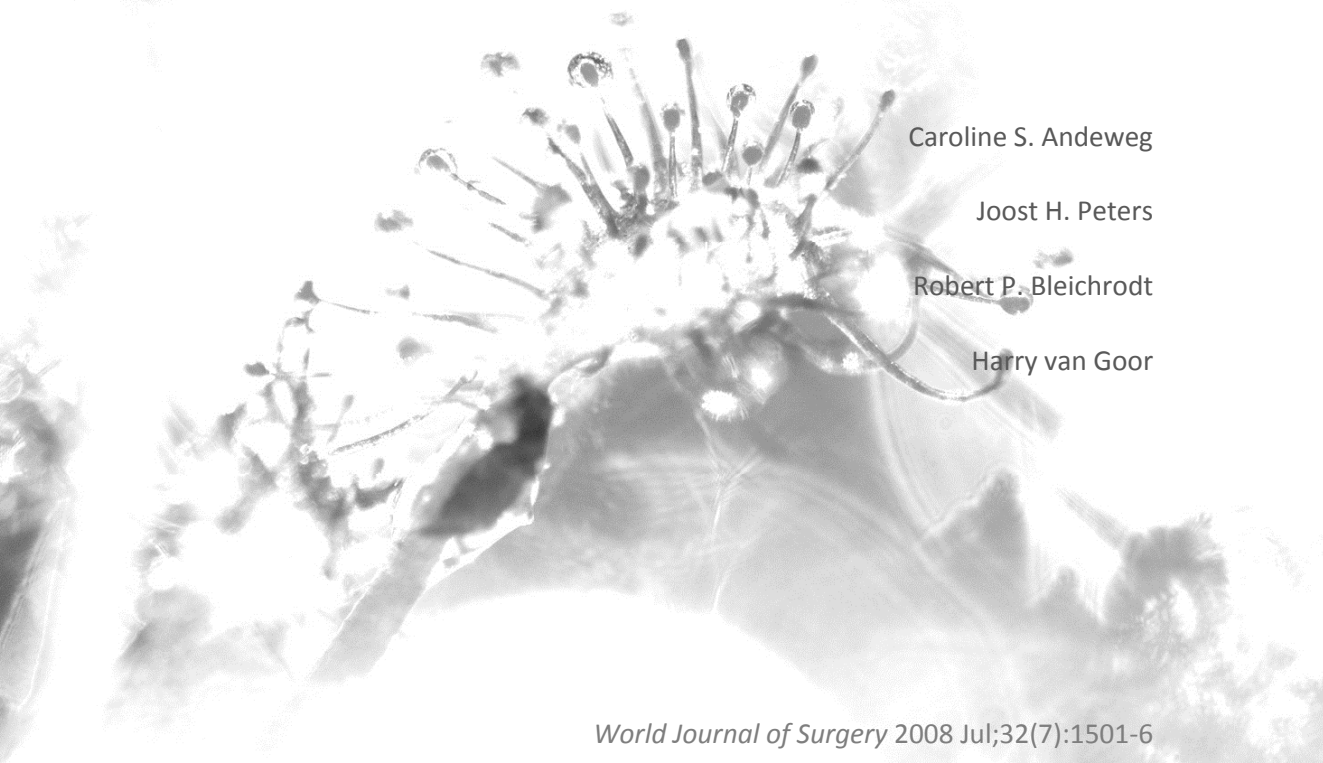
Table S1: Characteristics of included studies evaluating patients with diverticulitis

Reference	Design	Patients	Intervention	*N*	*N* after follow-up	Outcomes	Follow-up		Results
							before treatment	after treatment	
Simpson (2003)[14]	Cohort	Acute uncomplicated diverticulitis Proven diverticula by endoscopy or radiology	Conservative treatment	27	26	Pain (% of patients with episodes of mild to moderate abdominal pain)	No	Median 25 months	Episodes of mild to moderate abdominal pain: 69%
Vignati (1995)[53]	Cohort	Acute diverticulitis <50 years old Proven by radiology or operative findings	Antibiotic treatment	40	28	Bowel symptoms (mild symptoms: pain, diarrhea, constipation, avoidance of certain foods)	No	5-9 years	Symptom free; 58% Mild, persistent symptoms: 42%
Rodriguez (2010)[27]	Cohort	Uncomplicated diverticulitis Proven by CT	Antibiotic treatment	NR	24	Satisfaction (% of satisfied patients)	No	NR	Satisfied: 95%

[a] SF-36: Short Form 36; contains 36 items and measures QoL on 8 different dimensions. Each item is scored on a 0 to 100 range so that the lowest and highest possible scores are set 0 and 100, respectively.
[b] CACP: Chirurgische Arbeitsgemeinschaft für Coloproktologie; consists of 8 questions discussing faecal incontinence. A maximum score of 17 points means the best continence.
[c] Wexner constipation score: scoring system consists of 8 items reporting on constipation (associating) symptoms. Lowest score is 0 (no complaints), maximum score is 30 (worst)
[d] GIQLI: The Gastro Intestinal Quality of Life Index; a questionnaire that assesses bowel-related QoL. It consists of 36 items spread between the domains of symptoms, physical state, emotional and social functioning. Each of the questions can be answered with a score between 1 (the worst) and 4 (the best) and after summing a maximum score of 144 points can be achieved.
[e] EORTC-QLQ-CR 30: The European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-C 30; was originally developed to assess QoL in patients with cancer. This questionnaire consists of 30 items that can be divided in five functional scales, three symptom scales and six single items. The scores per scale can be summed and rescaled from 0 to 100, with a higher score indicating a better QoL
[f] IPSS: International Prostate Symptom Score; consists of 7 questions scored from 0 to 5 points concerning male urinary function, with a worst score of maximum 35 points.
[g] UDI: Urinary Distress Inventory; consists of 6 items scored from 0 to 3 points concerning female urinary function. Maximum score of 18 means very symptomatic.
[h] IEFF-5: International Index of Erectile Function; consists of 5 questions scored from 1 to 5 concerning erectile dysfunction. A score of >20 implies no erectile dysfunction.
[i] UFSS: Urinary Function Satisfaction Score; consists of a scale from 0 (complete satisfaction) to 6 (major discomfort) regarding urinary function.
[j] IS: Jorge-Wexner Incontinence Score; assesses faecal incontinence and score ranges from 0 (full continence) to 20 (total incontinence).
[k] FISI: Faecal Incontinence Severity Index; calculates incontinence severity by assessing leakage of gas, mucus, liquid or stool at varying frequencies. Scores range from 0 (no incontinence) to 61 (incontinence at least twice daily). FISI ≥ 25 was considered major incontinence.
[l] MBFI: Memorial Bowel Function Index; authors used a modified version of the MBFI scale and calculated an ''Emptying Score'' and a "Faecal Urgency Score''.
[m] VAS: Visual Analogue Score; a score of 0 was regarded as no discomfort and 100 as incapacitating discomfort
[n] CGQL: Cleveland Global Quality of Life; instrument is mainly used in patients with ulcerative colitis or Crohn's disease. It contains three items (current quality of life, current quality of health and current energy level) that can be scored on a scale of 0 to 10 (0: worst, 10: best). The scores can be added and the final CGQL utility score can be obtained by dividing the result by 30.
[o] DDSS: Ad Hoc Diverticular Disease Symptom Score; consists of 12 items of abdominal symptoms scored on a range from 0 to 3. A maximum score of 36 indicated very compromised patients.
[p] BSFS: Bristol Stool Form Scale; a seven-point scale that is used to describe stool consistency. (1= separate hard lumps, till 7=watery)
[q] GSS: Global Symptom Score; is a score of 10 individual gastro-intestinal symptoms most commonly associated with diverticular disease. Every symptom rates 0 (no symptoms) to 6 (severe complaints), with a maximum score of 60.
[r] IMAP: inferior mesenteric artery preservation

Chapter 8

Incidence and risk factors of recurrence after surgery for pathology proven diverticular disease



Caroline S. Andeweg

Joost H. Peters

Robert P. Bleichrodt

Harry van Goor

World Journal of Surgery 2008 Jul;32(7):1501-6

Abstract

Background

Diverticular disease is a common problem in Western countries. Rationale for elective surgery is to prevent recurrent complicated diverticulitis and to reduce emergency procedures. Recurrent diverticulitis occurs in about 10% after resection. The pathogenesis for recurrence is not completely understood. We studied the incidence and risk factors for recurrence and the overall morbidity and mortality of surgical therapy for diverticular disease.

Methods

Medical records of 183 consecutive patients with pathology-proven diverticulitis were eligible for evaluation. Mean duration of follow-up was 7.2 years. Number of preoperative episodes, emergency or elective surgeries, type of operation, level of anastomosis, postoperative complications, persistent postoperative pain, complications associated with colostomy reversal, and recurrent diverticulitis were noted. The Kaplan-Meier method was used to calculate the cumulative probability of recurrence. Cox regression was used to identify possible risk factors for recurrence.

Results

The incidence of recurrence was 8.7% with an estimated risk of recurrence over a 15-year period of 16%. Risk factors associated with recurrence were (younger) age (p<0.02) and the persistence of postoperative pain (p<0.005). Persistent abdominal pain after surgery was present in 22% of patients. Eighty percent of patients who needed emergency surgery for acute diverticulitis had no manifestation of diverticular disease prior to surgery. In addition, recurrent diverticulitis was not associated with a higher percentage of emergency procedures.

Conclusions

Estimated risk of recurrence is high and abdominal complaints after surgical therapy for diverticulitis are frequent. Younger age and persistence of postoperative symptoms predict recurrent diverticulitis after resection. The clinical implication of these findings needs further investigation. Results of this study support the careful selection of patients for surgery for diverticulitis.

Introduction

Diverticulosis is considered to be mainly a problem of old age, with a prevalence of 35-50%.[1, 2] About 10 to 25% of patients with diverticulosis will develop diverticular disease in their lifetime.[3, 4]

The clinical presentation of diverticular disease depends on the severity of the inflammatory process and whether complications are present. Complicated diverticulitis refers to the presence of perforation, obstruction and abscess or fistula formation. Between 25 and 55% of the patients with complicated diverticulitis will require surgery during their initial hospitalization.[5]

The current recommendation for patients with diverticular disease is elective surgery after the second documented episode of diverticulitis to prevent recurrent disease, because recurrence may lead to more complications and greater morbidity.[5-7] Recently however, the necessity and timing of elective surgery has been debated with respect to recurrent disease and prevention of major complications.[8, 9] Elective surgery for diverticular disease has failed when there is a recurrence that adversely affects the patients' well-being. In the literature recurrence rates after appropriate resection of the sigmoid vary between five and 11% and a substantial number of these patients even needs urgent reoperation.[10-14] Identifying patients at risk for failure of resectional therapy would help to better select patients for elective surgery. Thus far, the level of anastomosis and age have been associated with recurrence, but data confirming this are scarce.[11, 12]

The aim of this study was to assess the incidence and to identify possible risk factors for recurrence of diverticulitis in a large well-defined group of patients who underwent surgery for uncomplicated and complicated diverticulitis. Moreover, overall morbidity and mortality of surgical therapy for diverticular disease was evaluated.

Patients and methods

A consecutive series of patients operated for diverticulitis in our department between 1985 and 2003 were identified from the Dutch pathology computer database, using search terms "diverticular disease", "diverticulitis" and "diverticulosis". Medical records were reviewed and the following data were collected: number of preoperative episodes (number of episodes of diverticulitis requiring hospital admission before operation), emergency or elective surgery, type of operation (sigmoid resection, sigmoid resection with colostomy (Hartmann), left sided hemicolectomy, anterior resection (AR), AR with colostomy, miscellaneous), level of anastomosis (colorectal or colosigmoidal), post-operative complications, complications associated with colostomy reversal, and recurrent diverticulitis. Only major complications related to the surgical procedure and reoperations

were noted. Anastomotic leak had to be confirmed by either radiographic enema, CT-scan or by reoperation. Colostomies, time until reversal of the colostomy, and complications thereof were also recorded. Signs of active inflammation and the length of the resected specimen were noted from the pathology report. To complete follow-up, a questionnaire was sent to the patients' general practitioner (GP) and patients were interviewed by phone about recurrent diverticulitis, persistent complaints of left abdominal pain and, discomfort after initial surgery. Recurrent diverticulitis was defined as tenderness in the left lower abdomen, in combination with fever (temperature ≥38°C), or, alternatively, a sedimentation rate, C-reactive protein, or white blood cell count above normal values resulting into hospital admission. These findings had to be consistent with barium enema, colonoscopy, or CT findings. This study was conducted with the approval of the ethics board of our hospital and written informed consent was obtained from all patients in the study who received a questionnaire.

Statistical analysis

The t-test for two independent groups was used to test differences between patients with and without recurrence for statistical significance in case of quantitative variables. The Chi-square test was used in case of qualitative variables, and the Fisher exact test in case of 2 x 2 tables. To deal with the variable length of follow-up, the Kaplan-Meier product-limit method was used to calculate the cumulative time-related incidence of recurrent diverticulitis after resection. The endpoint used was the recurrence of diverticulitis after resection. For those patients with no recurrence, the date was considered to be right-censored at the date of death or the end of the observational period. This method calculates incidence curves over time by using follow-up data from all individuals in the cohort, regardless of duration of follow-up. A univariate Cox regression was used to study differences in the incidence curve for the following risk factors: age, gender, number of preoperative episodes, type of operation, emergency or elective surgery, level of anastomosis, length of resected specimen and persistent complaints after surgery. The hazard ratios with 95% confidence interval are presented. A value of *p* less than 0.05 was considered statistically significant.

Results

Demographics

Two hundred and twenty-two patients were identified by the computer database. Thirty-nine patients were excluded because of coexisting colonic malignancy or an alternative diagnosis (Crohn's disease or ulcerative colitis) in the definite pathologic examination report. Follow-up was complete in the remaining 183 patients. Patients' demographics are listed in *Table 1*. Mean duration of follow-up was 7.2 years (range = 0-18 years). Mean age at time of operation was 63 (range = 26-93 years). Seventy-three patients (40%) had emergency surgery including sigmoid resection with colostomy in 47 patients (64%) and

sigmoid resection with primary anastomosis in 26 patients (36%). Patients underwent elective surgery (60%) after completing diagnostic procedures, including barium enema (*n* = 101) and/or coloscopy (*n* = 48) and/or CT scanning (*n* = 4). All patients undergoing elective surgery had previous complaints suggesting diverticular disease with one to more than four documented episodes. The median documented number of episodes in the total group was 2 (range = 0-10). Signs of active inflammation were present in 166 patients (91%) at pathology.

Table 1: Patient demographics by recurrence of diverticulitis

Variable		***N***	**Recurrence**		**No recurrence**		***p* value**
			N	**%**	***N***	**%**	
Gender	Female	99	9	9	90	91	1.00*
	Male	84	7	8.3	77	91.7	
Operation	Elective	110	10	9	100	91	1.00*
	Emergency	73	6	8.2	67	91.8	
Number of preoperative episodes	0	63	3	4.8	60	95.2	0.07**
	1	16	3	18.8	13	71.2	
	2	88	7	8	81	82	
	3	11	3	27	8	73	
	≥ 4	5	0	0	5	100	
Type of operation	Sigmoid resection	88	10	11.4	78	88.6	0.53**
	Hartmann	62	4†	6.5	58	93.5	
	AR and primary anastomosis	12	2	11.1	10	88.9	
	AR and colostomy	6	0	0	6	100	
	Miscellaneous	10	0	0	10	100	
	Left-sided hemicolectomy	5	0	0	5	100	
Signs of active inflammation at pathology	Yes	166	13	7.8	153	92.2	0.17*
	No	17	3	17.6	14	82.4	
Persistent complaints	Yes	36	8	22.2	28	77.8	<0.01*
	No	147	8	5.4	139	94.6	
Level of anastomosis	Colorectal	21	3	14.3	18	85.7	0.04**
	Colosigmoidal	90	12	13.3	78	86.7	
	Colostomy	68	1	1.5	67	98.5	
	Other	4	0	0	4	100	
			Mean				
Age	Recurrence		54 years (range 33-75)				<0.02***
	No recurrence		64 years (range 27-93)				
Length of resected specimen	Recurrence		19.6 cm (range 12-34)				0.16 (3)
	No recurrence		17.1 cm (range 7-35)				

AR = Anterior Resection
* p value by Fisher exact test
** p value by Chi-square
*** p value by t-test
† Recurrence occurred in three patients after reversal of the colostomy and in one patient with a colostomy who later underwent a subtotal colectomy because of multiple diverticula in the entire colon

Postoperative morbidity and mortality

Early postoperative complications (within 30 days after primary surgery) requiring reoperation occurred in nine patients (4.9%). Indications for reoperation was anastomotic leak (*n* = 3), abscess formation with abdominal sepsis (*n* = 3), gauze left behind at initial laparotomy (*n* = 1), iatrogenic bowel perforation (*n* = 1), and fascial dehiscence (*n* = 1). The 30-day mortality rate for patients with emergency surgery was 9.5% (*n* = 7). No patients died within 30 days after elective surgery. Sixty-eight patients (37.2%) received a colostomy, which was reversed in 36 patients (53%) after a mean of 10 (range = 1-63) months. One patient died after colostomy reversal due to cardiogenic shock. Mean age of the group with colostomy reversal was significantly lower than the group who did not have colostomy reversal (60 vs. 69 years; t-test; p = 0.01). Three patients (8.3%) had anastomotic leak resulting in reoperation.

Persistent abdominal pain

Thirty-four patients died before the end of the observational period, leaving 149 patients available for long-term follow up. Of this group, 33 patients (22.1%) complained of persistent abdominal pain after primary resection. Signs of active inflammation were present at pathology in 29 of them (88%). One hundred and sixteen patients did not have persistent postoperative pain but signs of inflammation were present in a similar percentage (103 patients; 89%). The mean length of resected sigmoid in the group with persistent postoperative pain was 17cm compared to 17.5cm in patients without complaints. (t-test; p=0.15)

Recurrences

Recurrence rate was 8.7% (*n* = 16) and recurrences occurred after a mean of 3.2 (range = 0.5-12) years. Mean age at operation was significantly lower in the recurrence group than in the non-recurrence group (54 vs. 64 years; t-test; p<0.01). The type of previous operation performed in the recurrence group was resection of the sigmoid in ten cases; Hartmann's procedure in four cases and a low anterior resection in two cases. Six out of 16 (37.5%) were emergency procedures. Eight patients (50%) with recurrent disease were treated conservatively, because the complaints were mild in seven patients and the remaining patient was in poor general condition not favoring surgery. The other eight patients underwent a left-sided hemicolectomy because of multiple diverticula in three, a partial resection of the transverse colon after inflammation induced stenosis in two, and active inflammation in one patient. It was necessary to conduct a subtotal colectomy in two cases because of multiple diverticula in the entire colon. Only two patients (12.5%) with recurrent diverticulitis were operated on in an emergency setting. *Figure 1* shows Kaplan-Meier estimator of the cumulative time-related incidence of recurrence. The estimated risk of recurrent diverticulitis one year after operation was 3% (standard error (se) = 1.3), increasing to 8.2 % (se = 2.3) at 5 years, 12% (se = 3.0) at 10 years and 16% (se = 3.7) at 15 years.

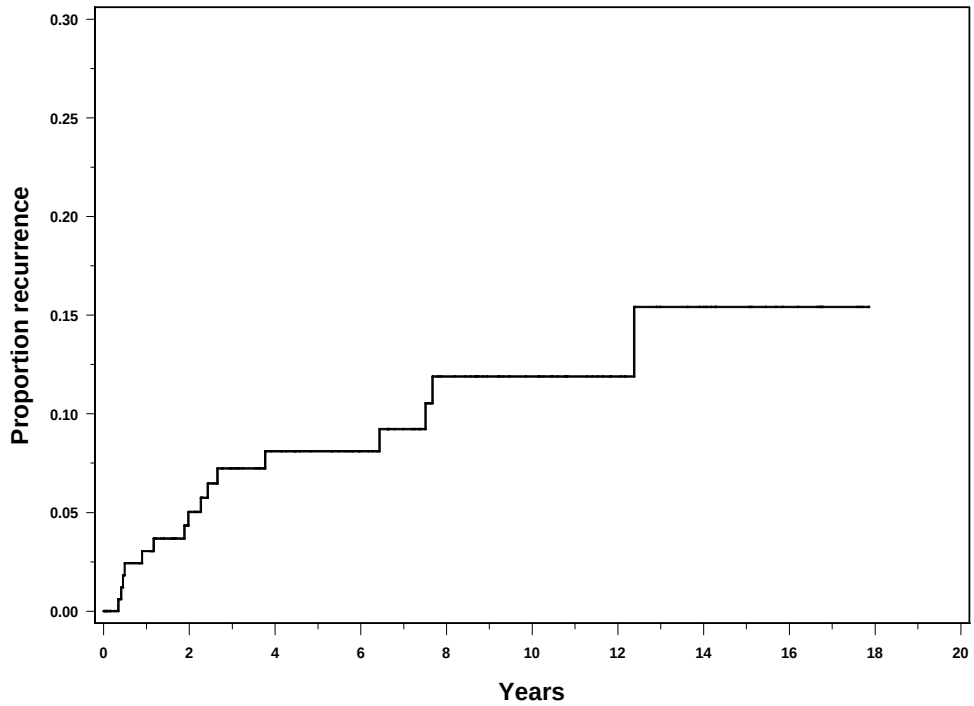


Figure 1: Cumulative incidence of recurrent diverticulitis after resection using the Kaplan-Meier method for time-related incidence. This method adjusts the incidence ratio to account for various lengths of follow-up and losses to follow-up.

Table 2 shows the hazard ratios (with 95% confidence interval) of risk factors for recurrent diverticulitis adjusted for length of follow-up using a univariate Cox regression. Age, level of anastomosis, and the persistence of postoperative symptoms appeared to be significant risk factors for recurrent diverticulitis. Younger age and persistent postoperative symptoms were significantly related to an increased risk for recurrence. This also held for either colorectal of colosigmoidal anastomosis compared to colostomy. A multivariate Cox regression showed that these were independent risk factors for recurrent diverticulitis.

Gender, elective or emergency surgery, type of operation and number of episodes were not significantly associated with a higher risk of recurrence.

Table 2: The hazard ratio with 95% confidence interval for recurrence of diverticulitis

Variable	Hazard ratio (95% CI)	*p* value
Gender		0.86
- Female	1.09 (0.41-2.94)	
- Male	1.00 (reference)	
Operation		0.60
- Elective	1.00 (reference)	
- Emergency	1.31 (0.47-3.61)	
Episodes (number)	1.20 (0.71-2.4)	0.49
Type of operation		0.34
- Sigmoid resection	1.00 (reference)	
- Hartmann	0.72 (0.23-2.30)	
- Anterior resection†	1.33 (0.29-6.09)	
- Miscellaneous‡	NE	
Signs of active inflammation at pathology		0.30
- Yes	0.48 (0.14-1.69)	
- No	1.00 (reference)	
Persistent complaints		<0.01
- Yes	4.76 (1.79-12.5)	
- No	1.00 (reference)	
Level of anastomosis		0.02
- Colorectal	11.35 (1.18-109.50)	
- Colosigmoidal	7.49 (0.97-57.63)	
- Other	1.00 (reference)	
Age (years)	0.96 (0.93-0.99)	0.02

CI: confidence interval
NE: not estimable
† Anterior resection with primary anastomosis and colostomy pooled
‡ Left-sided hemicolectomy and miscellaneous pooled

Discussion

Primary aim of this large and well-documented study was to calculate the cumulative incidence of recurrent diverticulitis in patients who underwent emergency or elective surgery for diverticulitis and to identify possible risk factors associated with recurrence in a large group of patients with histology-confirmed diverticulitis. Diverticulitis recurred in about 9% of the cases and in two thirds within five years after initial surgery. Young patients and those with abdominal complaints were significantly at risk for recurrent diverticulitis.

Data from the 1960s and 80s showed rates of clinically suspected recurrent diverticulitis after resection varying between 7% and 11%.[10, 11, 14] Slightly lower recurrence rates between 5% and 8% were found more recently, explained by the fact that recurrences had to be consistent with barium enema or CT-findings.[12, 13] Our overall recurrence rate agrees with that of others, but the advantage of our long-term data lies in the estimated risk of

recurrence adjusted for length of follow-up. The estimated risk of recurrence is 16% over 15 years, meaning that of every six patients risks a recurrence after resection.

Younger age was a risk factor for recurrence independent of the greater life time exposure to diverticulosis in the present study. The pathogenic mechanism in young patients with diverticular disease presumably differs from that in older patients, in whom age-related weakening of the colonic wall seems to play an important role. Recent findings of histological similarity between the colonic wall surrounding diverticula and biopsies of patients with inflammatory bowel disease are interesting in that they give a deeper understanding of potential pathogenic mechanisms of diverticula formation and diverticulitis in young patients.[15-17]

Abdominal symptoms persist after resection in up to 33% of the cases and are attributed by most authors to coexisting irritable bowel syndrome (IBS) based on considerable overlap between symptoms of both diseases.[3, 18] It cannot be ruled out that IBS accounted for a certain failure rate after surgery; however, this would be expected in patient groups lacking inflammatory changes in the resected specimens. Over 90% of resected bowel parts had histological signs of inflammation in our series, making IBS an unlikely cause for persistent complaints, which is further supported by the finding that postoperative abdominal complaints are an independent risk factor for recurrent diverticulitis. This implies that persistence of symptoms after resection for complicated diverticulitis should be taken seriously and properly be investigated by physicians.

It has been found that recurrence rates are lower if the total sigmoid had been removed and a rectal anastomosis had been made.[11, 12] We could not confirm this finding in the present study, wherein data on the level of anastomosis and type of operation were carefully extracted from the operative reports. Mean specimen length of 19.6cm and 17.1cm, respectively, did not significantly differ between the recurrence and non-recurrence groups, further suggesting that the extent of resection and type of anastomosis are not important factors for recurrence.

Elective surgical resection is advised after two episodes of uncomplicated diverticulitis, although recent reports suggest a more conservative and individualized approach.[19] The rationale for surgery is to prevent recurrent complicated diverticulitis and to reduce emergency procedures. We challenge this advice based on the findings that one of every six operated patient is at risk of recurrence, 22% of patients have persistent abdominal complaints, and 80% of patients, needing emergency surgery for acute diverticulitis had no manifestation of diverticular disease prior to surgery. Moreover, recurrent diverticulitis was not associated with a higher percentage of emergency procedures. Long-term morbidity related to colostomy reversal further emphasizes that patient selection for elective surgery should be done with caution.

Conclusion

After surgical therapy for diverticulitis the estimated risk of recurrence is high and abdominal complaints are frequent. Younger age and the persistence of postoperative symptoms predict a recurrence of diverticulitis after resection. The clinical implication of these findings needs further investigation. Results of this study support the practice of careful selection of patients who will undergo surgery for diverticulitis.

Reference list

1 Painter NS, Burkitt DP. Diverticular disease of the colon: a deficiency disease of Western civilization. Br Med J 1971; 2: 450-4.

2 Hughes LE. Postmortem survey of diverticular disease of the colon. I. Diverticulosis and diverticulitis. Gut 1969; 10: 336-44.

3 Parks TG. Natural history of diverticular disease of the colon. Clin Gastroenterol 1975; 4: 53-69.

4 Roberts P et al. Practice parameters for sigmoid diverticulitis. The Standards Task Force American Society of Colon and Rectal Surgeons. Dis Colon Rectum 1995; 38: 125-32.

5 Chautems RC et al. Long-term follow-up after first acute episode of sigmoid diverticulitis: is surgery mandatory?: a prospective study of 118 patients. Dis Colon Rectum 2002; 45: 962-6.

6 Maggard MA et al. Surgical diverticulitis: treatment options. Am Surg 2001; 67: 1185-9.

7 Hinchey EJ, Schaal PG, Richards GK. Treatment of perforated diverticular disease of the colon. Adv Surg 1978; 12: 85-109.

8 Sarin S, Boulos PB. Long-term outcome of patients presenting with acute complications of diverticular disease. Ann R Coll Surg Engl 1994; 76: 117-20.

9 Lorimer JW. Is prophylactic resection valid as an indication for elective surgery in diverticular disease? Can J Surg 1997; 40: 445-8.

10 Leigh JE, Judd ES, Waugh JM. Diverticulitis of the colon. Recurrence after apparently adequate segmental resection. Am J Surg 1962; 103: 51-4.

11 Benn PL, Wolff BG, Ilstrup DM. Level of anastomosis and recurrent colonic diverticulitis. Am J Surg 1986; 151: 269-71.

12 Thaler K et al. Determinants of recurrence after sigmoid resection for uncomplicated diverticulitis. Dis Colon Rectum 2003; 46: 385-8.

13 Thorn M, Graf W, Stefansson T, Pahlman L. Clinical and functional results after elective colonic resection in 75 consecutive patients with diverticular disease. Am J Surg 2002; 183: 7-11.

14 Wolff BG, Ready RL, MacCarty RL, Dozois RR, Beart RW, Jr. Influence of sigmoid resection on progression of diverticular disease of the colon. Dis Colon Rectum 1984; 27: 645-7.

15 Koutroubakis IE, Antoniou P, Tzardi M, Kouroumalis EA. The spectrum of segmental colitis associated with diverticulosis. Int J Colorectal Dis 2005; 20: 28-32.

16 Jani N, Finkelstein S, Blumberg D, Regueiro M. Segmental colitis associated with diverticulosis. Dig Dis Sci 2002; 47: 1175-81.

17 Peppercorn MA. The overlap of inflammatory bowel disease and diverticular disease. J Clin Gastroenterol 2004; 38: S8-10.

18 Munson KD, Hensien MA, Jacob LN, Robinson AM, Liston WA. Diverticulitis. A comprehensive follow-up. Dis Colon Rectum 1996; 39: 318-22.

19 Wong WD et al. Practice parameters for the treatment of sigmoid diverticulitis--supporting documentation. The Standards Task Force. The American Society of Colon and Rectal Surgeons. Dis Colon Rectum 2000; 43: 290-7.

Chapter 9

Guidelines of diagnostics and treatment of acute left-sided diverticulitis

Caroline S. Andeweg

Irene M. Mulder

Annelies Verbon

Richelle J.F. Felt-Bersma

Gert Jan van der Wilt

Harry van Goor

Johan F. Lange

Jaap Stoker

Marja A. Boermeester

Robert P. Bleichrodt

Digestive Surgery 2013 Aug 20;30(4-5):278-292

Abstract

Background
Incidence of acute left-sided diverticulitis (ACD) is increasing in the Western world. To improve the quality of patient care, a guideline for diagnosis and treatment of diverticulitis is needed.

Methods
A multidisciplinary working group, representing experts of relevant specialties, was involved in the guideline development. A systematic literature search was conducted to collect scientific evidence on epidemiology, classification, diagnostics and treatment of diverticulitis. Literature was assessed using the classification system according to an evidence-based guideline development method, and levels of evidence of the conclusions were assigned to each topic. Final recommendations were given, taken into account the level of evidence of the conclusions and relevant other considerations such as patient preferences, costs and availability of facilities.

Results
The natural history of diverticulitis is usually mild and treatment is mostly conservative. Although younger patients have a higher risk of recurrent disease, a higher risk of complications compared to older patients was not found. In general, the clinical diagnosis of ACD is not accurate enough and therefore imaging is indicated. The triad of pain in the lower left abdomen on physical examination, the absence of vomiting and a CRP>50mg/l has a high predictive value to diagnose ACD. If this triad is present and there are no signs of complicated disease, patients may be withheld from further imaging. If imaging is indicated, conditional computed tomography, only after a negative or inconclusive ultrasound gives the best results. There is no indication for routine endoscopic examination after an episode of diverticulitis. There is no evidence for the routine administration of antibiotics in patients with a clinically mild uncomplicated diverticulitis. Treatment of pericolic or pelvic abscesses can initially be treated with antibiotic therapy or combined with percutaneous drainage. If this treatment fails, surgical drainage is required. Patients with a perforated ACD resulting in peritonitis should undergo an emergency operation. There is an ongoing debate about the optimal surgical strategy.

Conclusions
Scientific evidence is scarce for some aspects of ACD treatment (e.g., natural history of ACD, ACD in special patient groups, prevention of ACD, treatment of uncomplicated ACD, and medical treatment of recurrent ACD), leading to treatment being guided by the surgeons' personal preference. Other aspects of the management of patients with ACD have been more thoroughly researched (e.g., imaging techniques, treatment of complicated ACD, elective surgery of ACD). This guideline of the diagnostics and treatment of ACD can be used as a reference for clinicians who treat patients with ACD.

Introduction

Left-sided diverticulosis of the colon is a common condition in Western society. The prevalence of diverticulosis coli depends on age and increases from about 5% around 40 years of age to 65% at the age of 85 years or older.[1, 2] It is estimated that approximately 25% of the patients with diverticulosis will develop an episode of acute colonic diverticulitis (ACD).[3] Patients with acute abdominal pain due to ACD impose an impressive burden to healthcare.[4] In the past years, a dramatic rise in the number of hospitalizations for ACD has been noted in the Netherlands. In 2009, 18,355 patients were hospitalized with ACD as compared to 13,655 patients in 2006. Meanwhile, expenditures for these hospital admissions in the Netherlands exceed 80 million euro per year.[5, 6] This rise in hospital admissions is also notable in other countries. A recent study from the United States showed an increase in hospital admissions during the period 1998-2005 of 26%, with the greatest rise in patients between 18 and 44 years of age.[4] In the Netherlands, women make up 60% of hospital admissions for ACD.[6] This difference in incidence of ACD between men and women has been noticed in other countries as well. Patients younger than 50 years of age with ACD are predominantly men, whereas in the age group of 50-70 years there seems to be a preference for women.[7-11] Patients with mild (recurrent) diverticulitis are usually treated by a general practitioner or on an outpatient basis, which makes it difficult to accurately determine the true incidence and recurrence rates of diverticulitis.

Although ACD is a very common disease, the clinical diagnosis remains a challenge for clinicians and health care researchers. Diagnostics and treatment of diverticulitis are mostly characterized by doctors' personal preferences rather than standardized evidence-based protocols. This is mainly due to the fact that there is a large amount of conflicting and low quality evidence in publications regarding diverticulitis. To provide doctors and other health care providers support in clinical decision-making, practice guidelines can be developed. Guidelines are applicable nationwide, but if based on international literature can be applicable to developed countries. Therefore, a multidisciplinary working group developed national guidelines including the epidemiology, classification, diagnostics and treatment of ACD in all its aspects based on an evidence-based review of the international literature.

Methods

The guideline was written under the auspices of the Netherlands Society of Surgery, in collaboration with the Netherlands Societies of Internal Medicine, Gastroenterologists, Radiology, Health Technology Assessment and Dieticians. The working group consisted of four surgeons, a gastroenterologist, a radiologist, an internist specialized in infectious diseases, a dietician and an epidemiologist and statistician. Participation of a patients'

representative in the working group was not possible because a patient association for patients with ACD does not exist in the Netherlands. The working group defined the following sections of relevance: terminology and classification, epidemiology, special patient groups with ACD, prevention of recurrent ACD, clinical diagnosis and radiological imaging, colonoscopy, treatment of uncomplicated and complicated ACD, elective surgery and medical treatment in patients with ACD.

Search strategy

Systematic searches of the Medline and Embase database were performed using the keywords relevant to each section. Terms relevant to each section of the guideline were mapped to Medline Subjects Headings (MeSH) terms, as well as being searched for as text items. Relevant keywords and search strategies can be found in *Appendix 1*. Articles describing randomized controlled trials and systematic reviews were searched for using the methodological filters of the Scottish Intercollegiate Guidelines Network (*https://www.sign.ac.uk/methodology/filters.html*). Different date censoring and limitations were applied according to the relevance of each keyword. Only publications in English, France, German and Dutch were retrieved and read in full. The bibliographies of included articles were subsequently hand-searched for other relevant references and experts in the field were asked if they found any relevant reports missing.

Critical appraisal

Articles selected to support recommendations were assessed using the national classification system for evidence-based guideline development (*http://www.cbo.nl*), which is equivalent to the levels of evidence as published by the Centre of Evidence Based Medicine of the University of Oxford (*http://www.cbem.net*). (*Table 1*) Articles were classified according to the type of article and individually assessed for methodological quality using the GRADE method as proposed by the GRADE working group. That working group has developed a common, sensible and transparent approach to grading quality of evidence and strength of recommendations (*http://www.gradeworkinggroup.org*).

The main literature on which the conclusion for each relevant topic is based, is stated with the conclusion, accompanied by the level of evidence (*Table 2*). The final recommendations are based on the available evidence from literature, also taking into account 'soft' factors such as patient preferences, costs and availability of facilities. Recommendations can be strong (we can be confident about the recommendation, level I) to weak (we cannot be confident, level IV). A concept guideline was sent to all involved societies for comment and approval after which internal consensus was reached between the members of the working group. Amendments were made based upon these comments, leading to the final version of the guideline 'Diagnostics and treatment of Acute Colonic Diverticulitis', as approved by all societies.

Table 1: Classification of evidence

Level of evidence	Interventional research	Studies concerning diagnostic accuracy	Studies on complications or side-effects, etiology, prognosis
A1	Systematic review/ meta-analysis of at least 2 independently performed level A2 studies		
A2	Double blind controlled randomized comparative clinical trial of good study quality with adequate number of study participants	Diagnostic test compared to reference test; criteria and outcomes defined in advance; assessment of test results by independent observers; independent interpretation of test results; adequate number of consecutive patients enrolled; all patients subjected to both tests	Prospective cohort with sufficient amount of study participants and follow-up, adequately controlled for confounders. Selection in follow-up has been successfully excluded
B	Comparative studies, but without all the features mentioned for level A2 (including patient-control studies, cohort studies)	Diagnostic test compared to reference test, but without all the features mentioned in A2	Prospective cohort study, but without all the features mentioned for level A2 or retrospective cohort study or case-control study
C	Non-comparative studies		
D	Expert opinion		

Table 2: Grading of the conclusions according to the level of evidence

Level	Conclusion based on
1	Systematic review (A1) or at least 2 independent studies with evidence level A2 (*There is evidence that…)*
2	One study with evidence level A2 or at least 2 independent studies with evidence level B (*It is likely that …*)
3	One study with evidence level B or level C (*There are indications that…*)
4	Expert opinion (*The working group recommends….*)

Results

Terminology and classification

The term “diverticular disease” used in Anglo-Saxon literature is made up of a spectrum of conditions all related to diverticulosis of the colon. Some use the term “diverticular disease” for patients having symptoms associated with diverticulosis and distinguish diverticulitis as a different entity, whereas others include diverticulitis and diverticular bleeding in the term “diverticular disease”. The lack of uniformity in terminology results in difficulties interpreting and comparing findings between studies. It seems best to use the term “diverticulosis coli” and to distinguish between uncomplicated (asymptomatic) and complicated (symptomatic) diverticulosis. Patients with uncomplicated diverticulosis have

no symptoms, and therefore the term asymptomatic diverticulosis is also used. Complicated diverticulosis coli, or symptomatic diverticulosis coli, is the complete spectrum of symptoms that can arise in patients with diverticulosis coli. This includes patients with (chronic) persistent abdominal pain, acute colonic diverticulitis and diverticular bleeding. ACD refers to inflammation of diverticula. Uncomplicated ACD is referred to when inflammation of one or more diverticula leads to an inflammatory process without perforation or abscess formation. Complicated diverticulitis is associated with abscess formation, perforation or fistula formation. Recurrent episodes of ACD may result in stenosis and obstruction or fistula to nearby organs (mostly bladder) or the skin; these late complications are also referred to as complicated diverticulitis.

To classify acute diverticulitis, Hinchey et al.[12] proposed a classification system, which is currently used in clinical practice in a modified version (*Table 3*).[13] The Hinchey classification has traditionally been used to distinguish four stages of complicated diverticulitis. Wasvary et al.[13] introduced stage 0, clinically mild diverticulitis, and differentiation in stage I between limited pericolic inflammation (stage Ia) and abscess formation smaller than 5cm in the proximity of the primary inflammatory process (stage Ib). This broadened the original Hinchey classification by not only addressing perforated disease, but also including mild clinical disease. [13, 14] After the introduction of computed tomography (CT) for diagnosing acute diverticulitis, several radiologic classification systems were proposed additionally.[15, 16] CT findings were correlated with the modified Hinchey scores to come to uniform reporting of CT findings (*Table 3*).

Table 3: CT findings according to Kaiser et al 2005[52]

Modified Hinchey classification		**Accompanying CT findings**
Stage 0	Clinically mild diverticulitis	Diverticula with or without wall thickening of the colon
Stage Ia	Confined pericolic inflammation and phlegmonous inflammation	Colonic wall thickening with inflammatory reaction in pericolic fatty tissue
Stage Ib	Abscess formation (<5cm) in the proximity of the primary inflammatory process	Alterations as stage Ia + pericolic or mesocolic abscess formation
Stage II	Intra-abdominal abscess, pelvic or retroperitoneal abscess, abscess distant from the primary inflammatory process	Alteration as stage Ia + distant abscess formation (mostly pelvic or interloop abscesses)
Stage III	Generalized purulent peritonitis	Free air with local or generalized free fluid and possible thickening of the peritoneum
Stage IV	Faecal peritonitis	Similar findings to stage III

Conclusion and recommendations

Uniform terminology is needed in patients with diverticulosis coli. A distinction is made between uncomplicated (asymptomatic) diverticulosis and complicated (symptomatic) diverticulosis. The latter term is used for the complete spectrum of symptoms that can arise in patients with diverticulosis coli (level 4).

Epidemiology

Researching the natural history of ACD is hampered by a number of factors. There is no registry of patients regarding the natural course of the disease. Most patients with recurrent episodes of ACD have had elective surgery after two episodes of ACD, which makes it difficult to determine true recurrence rates in patients with ACD.[17] Recurrence rates of ACD, in which a recurrence is based on the clinical diagnosis without imaging, varies between 9%-29% (level C[9, 18-23]). The accuracy of the diagnosis in these studies is questionable, because of the lack of a good reference test. There are two studies with adequate reference testing that give information on the natural disease history, which report an estimated chance of recurrence of 9% (level C[24]) and 23% (level C[25]). The highest risk of recurrence seems to be in the first year (10%) and drops to approximately 3% in the years thereafter (level C[21]). The real risk of recurrence is underestimated in these studies; recurrence rates apply invariably to a selected group of patients, namely patients with symptoms severe enough for hospital admittance. The majority of recurrences tend to be mild recurrences that can be managed by conservative treatment (level C[9, 18, 19, 21-25]). Based on recent studies, most perforations do not occur after recurrences, but after the first attack of ACD (level C[26-33]). Multiple recurrences were not associated with a higher chance of mortality, nor did they lead to a higher chance of complicated disease (level C[26-33]).

Conclusions and recommendations

The natural history of diverticulitis is usually mild and most patients are treated successfully by conservative means (level 3). Multiple recurrences do not lead to a higher risk of complicated diverticulitis (level 3). Patients should be informed of an approximately 25% risk of recurrence after an initial episode of ACD (level 3).

Special patient groups

Young patients

The definition of young age in patients with ACD is either below 40 or 50 years. Of all patients hospitalized for ACD, 18-34% are younger than 50 years.[34, 35] Some authors have reported that young patients have an increased risk of complications and recommend early resection.[8, 36-38] This assumption is based on outdated studies, in which 48-88% of the patients who had surgery for suspected diverticulitis appeared to have another diagnosis at surgery. Recent studies, using CT to diagnose ACD, did not find a higher risk of complications in young patients (level C[7, 18-20, 25, 34, 35, 39, 40]). In young patients the reported

high risk of recurrent disease is caused by a higher accumulated risk due to higher life expectancy rather than absolute risk (level C[18-20, 40]). There is no evidence that younger patients should be treated different than older patients (level C[20, 25, 34, 35, 39, 40]).

Immunocompromised patients
In patients with a compromised immune system an increased incidence of ACD has been reported compared to healthy individuals, especially in patients with kidney failure, organ transplant patients and patients using corticosteroids (level C[41, 42]). These patients were significantly more often diagnosed with complicated diverticulitis (level C[28, 42-45]). Screening and prophylactic sigmoid resection is not routine for patients waiting for organ transplantation (level C[42, 46]). Patients with immune deficiency caused by HIV infection, diabetes, malignancy or chemotherapy do not have an increased risk of complicated diverticulitis (level C[47, 48]). Some reports indicate an increased risk of ACD in obese patients, but evidence is inconsistent (level B[49] and level C[50, 51]).

Conclusions and recommendations
Young patients do not have a more aggressive course of ACD than older patients (level 3). Young patients have a higher risk of recurrent disease, but the absolute risk difference is relatively small (level 3). Screening for diverticulosis in immunocompromised patients or patients awaiting organ transplantation in order to perform a profylactic colonic resection is not effective (level 3).

Prevention of diverticulitis
There are indications that people with a healthy lifestyle, characterized by physical exercise, fiber rich diet, limited intake of red meat, low alcohol consumption and non-smoking, have a decreased risk of diverticulitis (level B[52] and level C[53]).

Conclusions and recommendations
Counselling patients on risk factors for developing diverticulosis should be included in treatment protocols (level 3).

Clinical diagnosis and radiological imaging

Clinical diagnosis
The clinical diagnosis of ACD, based on reported complaints, physical examination and laboratory results, is correct in 43%-68% of patients (level B[54, 55] and level C[56, 57]). To improve diagnostic reliability a clinical decision rule and a clinical scoring system for diagnosing ACD, using logistic regression have been published.[54, 55] Reliable independent individual risk factors for ACD in both studies were pain only in the left lower abdominal quadrant, the absence of vomiting and a CRP level >50mg/l. If all three criteria were met, 97% of the patients had ACD (level B [54, 55]).

Radiological imaging

Radiological imaging techniques that are used for the diagnosis of ACD are soluble contrast enemas, ultrasound (US), CT and magnetic resonance imaging (MRI). Soluble contrast enemas are obsolete for diagnosing ACD due to low accuracy and the inability to determine the extent and complications of the disease (level A2[58] and level B[59]). The most used US technique to examine patients with suspected ACD is the graded compression procedure. With this technique, interposing fat and bowel can be displaced or compressed by means of gradual compression to show underlying structures.[60] US is a real-time dynamic examination with wide availability and easy accessibility. The use of CT in evaluation of patients with ACD has increased to a large extent. CT has the advantage of delineating the extent of the extra luminal disease process, has an unlimited view and may also direct therapeutic intervention in case of complicated disease, e.g., US-guided percutaneous drainage of intra-abdominal abscesses. CT criteria are also used as a prognostic tool to determine the risk of complications during conservative treatment.[16, 61] The most used diagnostic criteria to diagnose ACD with US and CT are increased thickness of the colonic wall, pericolic fat stranding and presence of inflamed diverticula. To optimally depict diverticulitis the use of intravenous, oral and/or rectal contrast agents are advised.[62] Studies report high diagnostic sensitivity and specificity for both US (92% and 90%, respectively) and CT after negative or inconclusive US (94% and 99%, respectively; level A1[63, 64]). More recently, in a large prospective series of unselected patients with acute abdominal pain at the emergency department, for which imaging was indicated by the treating physician, a much lower sensitivity of 61% (52-70%) was found for US, whereas the sensitivity of CT for the diagnosis of ACD was 81% (74-88%). Sensitivity can be increased up to 94% by performing US first, and CT only in case of a negative or inconclusive US. This step-up approach lowered the exposure to ionizing radiation for the study population (level A2[65, 66]). Besides the known differences between the techniques (availability, costs, reproducibility and inter observer differences) exposure to radiation during CT and contrast induced nephropathy are a concern.[60] MRI has the advantage that no ionizing radiation and intravenous contrast medium are needed to reach a higher soft tissue contrast than CT. MRI is increasingly used in the acute setting for patients with acute abdominal pain, but accuracy data are still limited. Based on studies with small numbers of patients, sensitivity and specificity of MRI for diagnosing ACD vary between 86% and 100% and 88% and 100% (level B[67, 68] and level C[69, 70]).

Conclusions and recommendations

In general, the clinical diagnosis of ACD is not sufficiently accurate and therefore radiological imaging is indicated in these patients (level 2). Patients with mild symptoms and no signs of complicated ACD, and the combination of pain in the lower left abdomen on physical examination, the absence of vomiting and a CRP >50mg/l may be withheld from initial imaging for diagnosing ACD (level 2). If imaging is indicated, a conditional CT after negative or inconclusive ultrasound is the most appropriate approach in diagnosing ACD (level 2).

Colonoscopy

Colonoscopy is not recommended in the acute phase to diagnose ACD (level B[71] and level C[72]). Although proven feasible in one prospective study, it is rarely needed in the acute phase (level C[73]). Possible difficulties of colonoscopy in the acute phase are incomplete examination due to pain, stenosis and incomplete bowel preparation. Discouragements to perform colonoscopy in the acute phase are based on the hypothesis that insufflation of air is associated with the risk of converting a sealed perforation to a free perforation.[73-75]

Colonoscopy is usually done 6 weeks after an episode of ACD, to exclude a colonic malignancy. The lifetime risk of developing colonic cancer is approximately 5%. It is unlikely that patients after an episode of ACD have an increased risk of the development of colonic cancer (level B[76, 77] and level C[78]) Although safe, routine performance of a colonoscopy in asymptomatic patients after an episode of ACD, to exclude other diagnoses was found not to be helpful (level B[71, 79, 80]).

Conclusions and recommendations

Colonoscopy in the acute phase of diverticulitis is not recommended for diagnostic purposes (level 3). There is no place for routine endoscopic examination after an episode of ACD (level 2).

Treatment of uncomplicated diverticulitis

Most patients with uncomplicated diverticulitis (Hinchey 0 or Ia) can be treated conservatively with a success rate of 93%-100% (level C[15, 81-86]). Conservative treatment includes antibiotics, starvation and bed rest in almost all studies. There is no evidence that bed rest, dietary restrictions or laxatives, positively influence the treatment outcome of ACD. In patients who do not tolerate oral feeding it is recommended to start parenteral feeding when oral feeding is not to be expected within three days (level D[87]). Almost all international guidelines advise the use of antibiotics for the treatment of diverticulitis. [17, 88-91] However, there is no evidence that routine administration of antibiotics influences the course of uncomplicated diverticulitis (level A2[92] and level B[79]). Oral administration of antibiotics seems equally effective to intravenous administration (level B[93]). Intravenous administration over 4 days is equally effective as 7 days (level B[84]). A recent prospective randomized clinical trial did not find a reduction of abscess formation, perforation and recurrence rates with the use of antibiotics.[92] The use of antibiotics seems appropriate in patients presenting with signs of generalized infection (temperature >38.5°C), affected general condition or signs of bacteraemia or septicaemia and in immunocompromised patients.

Analgesia is part of the treatment of patients with ACD. There is no evidence that acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) or morphinomimetics have a negative effect on the course of an episode of ACD. Multiple studies found that patients on home NSAID medication present more often with complicated diverticulitis,

i.e. perforation (level C[48, 94-97]). The (adverse) effect of NSAIDs started as an analgesic in patients with uncomplicated ACD has not been studied. Morphinomimetics can be safely administered to patients with acute abdominal pain without negatively affecting the diagnostic accuracy of clinical evaluation (level A2[98, 99]).

Conclusions and recommendations
There is no evidence that bed rest, dietary restrictions or laxatives influence the treatment of ACD (no evidence). There is no evidence that antibiotics should be routinely administered to patients with uncomplicated diverticulitis (level 2). Antibiotic treatment is recommended when signs of generalized infection (temperature >38.5°C) and affected general condition or signs of bacteraemia or septicaemia are present (level 4). Antibiotic treatment is recommended in immunocompromised patients (level 4).

Treatment of complicated diverticulitis

Hinchey Ib and II
There are no high-quality reports on the management of patients with ACD and abscess formation (Hinchey Ib and II); therefore no consensus has been reached about the most optimal treatment strategy. Since the introduction of broad-spectrum antibiotics and improvement in US- and CT-guided percutaneous drainage techniques, alternatives to surgery have become available. Conservative treatment with antibiotics is successful in up to 73% (95% CI: 66.3-78.9) of patients presenting with an abscess of less than 4 to 5cm in diameter (level C[16, 18, 100-104]). When conservative treatment fails, percutaneous drainage should be performed, which is successful in up to 81% (95% CI: 73.7-89.1) of patients (level C[15, 16, 100-104]). The risk of failure of conservative treatment is higher in patients with abscesses larger than 4-5cm than in patients with smaller abscesses (level C[15, 16, 100-104]).

Hinchey III and IV
Peritonitis is the most life-threatening complication of ACD, with a mortality of 14%.[105, 106] Perforation of the colon to the intra-abdominal cavity results in a purulent or faecal peritonitis. Perforation is a relative rare complication with an incidence of 3.5 per 100,000 individuals per year.[107] In a large population based study from the United States, only 1.5% of patients with ACD were found to have a perforation, and 9.6% were found to have an abscess.[108] Peritonitis is a progressive disease leading to general signs of illness, expressed in organ dysfunction or organ failure caused by bacteraemia and septicaemia. Prevention of these events by early intervention, i.e., aggressive resuscitation preventing inadequate tissue perfusion and oxygenation, the administration of broad spectrum antibiotics and elimination of the source of infection is the keystone of sepsis treatment.[109] Early treatment in patients with peritonitis significantly improves outcome.[109-111] No evidence-based advice can be provided for the indications for surgery in patients with perforated diverticulitis, but the indication seems self-evident.

Operative therapy

There are different surgical options for patients with Hinchey III and IV peritonitis: diverting colostomy, Hartmann's procedure or primary resection with anastomosis, and laparoscopic lavage with drainage of the abdominal cavity. Hartmann's procedure is the most performed, which is a two stage procedure involving resection of the diseased colon, closure of the distal rectal stump and construction of an end colostomy. In the second stage the colostomy is reversed, however restoration of the bowel continuity is not performed in up to 55% of patients due to operative risks.[112] Alternatively, resection with primary anastomosis, with or without a protective ileostomy or colostomy, can be performed. A diverting ileostomy or colostomy combined with intra-operative irrigation of the afferent colon can be performed to reduce the rate of symptomatic complications in case anastomotic leakage (level B[113, 114]) Studies comparing mortality, morbidity, wound complications, operation time and antibiotic treatment of Hartmann's procedure and primary anastomosis did not show any significant differences. However, most studies were prone to selection bias: patients were not randomized for Hartmann's procedure or primary anastomosis and patient groups were not comparable on patient characteristics and disease severity. It is likely that the choice of operation is influenced by patient conditions and peroperative findings. Nevertheless, there are indications that Hartmann's procedure and primary anastomosis have comparable outcomes (level B[113, 115, 116]). However, in critically ill patients, hemodynamic instability is a relative contraindication for a primary anastomosis. Due to administration of inotropes to maintain sufficient blood pressure, splanchnic perfusion can be reduced leading to increased risk of anastomotic leakage. This hypothesis has been confirmed (mainly in animal experiments) in studies on anastomotic healing in general surgery, although not after resection for diverticulitis. Faecal contamination of the abdominal cavity is thought not to be a contraindication for construction of a primary anastomosis.[117] Another treatment option in patients with purulent peritonitis is laparoscopic lavage and drainage of the abdominal cavity in which the colon is not resected. In nonrandomized series, hampered by patient selection, laparoscopic treatment accompanied by intravenous antibiotics seems to be an effective and safe treatment in Hinchey III patients (level C[57, 118]). However, the results of the first randomized trial need to be reviewed for a definite conclusion.[119]

Conclusions and recommendations

Smaller abscesses (<4-5cm) can be treated with antibiotics alone, whereas larger abscesses can best be treated with percutaneous drainage combined with antibiotic treatment (level 3). Operative treatment is considered standard therapy for patients with Hinchey III and IV diverticulitis (no evidence). In hemodynamically stable patients with acute diverticulitis and an indication for operative treatment, primary anastomosis with or without a diverting ileostomy or colostomy is preferred over Hartmann's procedure (level 2). In patients with Hinchey III diverticulitis, the safety and efficacy of treatment with laparoscopic peritoneal lavage is uncertain and remain so until the results of the first randomized trial on the subject become available (level 3).

Elective surgery

The American Society of Colon and Rectal Surgeons (ASCRS) state in their most recent guideline that elective sigmoid resection after recovery from ACD should be made on a case-by-case basis.[90] This advice differs significantly from the previous advice, given 6 years earlier, in which a plea for elective surgery after two episodes of diverticulitis was proposed.[120] Recent data on the natural history of diverticulitis has shown that recurrent episodes of diverticulitis mostly run a benign course and only 5.5% of the patients with recurrent hospitalizations for diverticulitis are subjected to emergency surgery.[20] Moreover, most patients who present with complicated diverticulitis do so at the time of their first attack (level C[26, 121, 122]) Recurrent diverticulitis even seems to reduce the risk of perforation, possibly due to adhesion formation caused by inflammation. Therefore, a policy of elective sigmoid resection after recovery from uncomplicated ACD does not decrease the likelihood of later emergency surgery and the number of previous episodes itself is no longer an indication for elective sigmoid resection (level C[18, 26, 33, 113, 121-123]) Persistent colonic symptoms, particularly abdominal pain, have been reported in patients after episodes of diverticulitis. It has been suggested that this pain represents increased visceral sensitivity.[124] These patients might benefit from early colonic resection.

After elective sigmoid resection there is a risk of anastomotic leakage, stoma formation, morbidity and mortality. Despite resection, even recurrent diverticulitis and continuing complaints have been described. Patients with immune deficiencies might benefit from early resection since they have a greater risk of perforations and a complicated course of recurrent episodes of diverticulitis (level C[18, 33, 121, 122]).

Elective sigmoid resection for complicated diverticulosis can be performed either with an open or laparoscopic approach. Two randomized trials favor laparoscopic surgery over open surgery. In the 'Sigma trial', significantly more complications, higher pain scores and longer hospital stay were found among patients with open surgery. Operating time was significantly longer in the laparoscopic group, with a conversion rate of 19%. Quality of life was significantly better after six weeks, but did not differ after 6 months (level A2[125]). The study by Gervaz et al.[126] also had equal long-term results, except for the cosmetic outcome, which was better in the laparoscopic group. No difference was found considering ventral hernia, patient satisfaction, quality of life or total costs (level A2). Laparoscopic surgery provides a faster functional recovery than open sigmoid resection and possible less chance of complications, but the long-term advantages of laparoscopic sigmoid resection are not evident yet (level A2[125, 126] and level B[127-131]). Both the Sigma trial and the Gervaz study did not use the Enhanced Recovery after Surgery (ERAS) principles, which are now widely adopted in the perioperative care of patients with abdominal surgery. The ERAS program reduced the risk of complications and hospital stay of open surgery to a large extent.[130] In addition, laparoscopic surgery is often done by dedicated surgeons, while open surgery is usually performed by a much larger group of surgeons, possibly influencing the results.

To reduce the risk of recurrent diverticulitis, the sigmoid should be resected up to the proximal rectum (level C[131, 132]). There is no evidence for the optimal proximal resection margin; however a resection as limited as possible in soft compliant bowel is recommended.[90]

Conclusions and recommendations
Patient-related factors, not so much the number of previous episodes of diverticulitis, should play the most important role in selecting patients who might benefit from elective sigmoid resection (level 3). If appropriate laparoscopic expertise is present, laparoscopic surgery for recurrent episodes of diverticulitis might be favored over open sigmoid resection in terms of short-term outcome, but no long-term benefits have been reported (level 1). During elective sigmoid resection, the part of the colon resected proximally to the inflammatory process should be as limited as possible with the proximal rectum as distal margin (level 3).

Medical treatment of recurrent diverticulitis
Traditionally, fiber-enriched diets in patients with diverticulitis have been considered to prevent recurrent episodes of ACD. However, randomized clinical trials on fiber-enriched diets in patients with ACD have inconsistent results.[133] A recently published systematic review of high-fiber dietary therapy could not include any studies concerning prevention of diverticulitis with a high-fiber diet.[134] Despite the lack of evidence, high daily fiber intake is recommended as treatment in various guidelines.[17, 88, 91, 135] Since obesity and smoking are associated with an increased risk of complications of diverticulitis, weight reduction and cessation of smoking can have a favorable influence on prevention of recurrent diverticulitis (level B[51, 136]). Although evidence on lifestyle advices to prevent recurrent episodes of ACD is missing, it is likely that the same measures to prevent ACD also apply to patients after an episode of ACD. Hence, a healthy lifestyle, characterized by physical exercise, fiber-rich diet, little intake of red meat, low alcohol consumption and non-smoking are advised in patients after an episode of ACD (level B[52] and level C[53]).

Recently, new theories about similarities between ACD and inflammatory bowel disease have been proposed, leading to new treatment possibilities, such as probiotics, antibiotics and anti-inflammatory agents.[137] Regarding drug treatment, intermittent administration of a non-absorbable antibiotic (rifaximin) after an episode of acute diverticulitis decreased the chance of readmission by 50% and of recurrent diverticulitis by 73% (level B[138]). Prevention of recurrent disease is more effective when 5-aminosalicylic acid (mesalazine) is combined with rifaximin, compared to rifaximin alone (level A2[139] and level B[140]). Furthermore, a combination of probiotics and anti-inflammatory medication is preferred over treatment with probiotics alone (level A2[141]).

Residual complaints after an episode of diverticulitis occur often and medical treatment can reduce symptoms. In these patients a trial period of intermittent administration of a

nonabsorbable antibiotic with mesalazine or probiotics should be considered. Especially since there is little risk from treatment by nonresorbable antibiotics or mesalazine combined with probiotics, while mortality and morbidity of operative treatment are substantial.

Conclusions and recommendations
The working group advises to give lifestyle advice to patients following an attack of diverticulitis, focusing on increasing daily fiber intake, weight reduction, cessation of smoking and increasing physical activity (level 4). Nonabsorbable antibiotics seem to reduce the risk of recurrent episodes of diverticulitis (level 3). The combination of 5-aminosalicylic acid and rifaximin is more effective than rifaximin alone in the prevention of recurrent episodes of diverticulitis (level 2). The working group opinion is that in patients with recurrent diverticulitis or patients with residual complaints following an episode of diverticulitis, in which other pathology has been excluded, a trial period of intermittent mesalazine, with or without a combination of an oral nonresorbable antibiotic or probiotic, should be considered (level 4).

Conclusion

This review of guidelines for diverticulitis summarizes the extensive literature available on epidemiology, prevention, diagnosing and treatment of patients with acute diverticulitis in all its aspects. The guideline was developed in order to standardize the treatment of patients with acute diverticulitis and to provide clinicians who deal with patients with diverticulitis on a daily basis, with an evidence-based medicine approach in treating and counseling patients. Despite a large amount of literature, not all topics were equally well addressed. Nevertheless, this review is the best evidence based approach currently available. The results of well-designed randomized studies will become available in the near future and give more insight in the optimal treatment of patients with acute diverticulitis of the colon.

Reference list

1 Painter N. S., and Burkitt D. P., 1975, "Diverticular disease of the colon, a 20th century problem", Clin Gastroenterol, 4(1), p. 3-21.

2 Parks T. G., 1975, "Natural history of diverticular disease of the colon", Clin Gastroenterol, 4(1), p. 53-69.

3 Schoetz D. J., 1999, "Diverticular disease of the colon: a century-old problem", Dis Colon Rectum, 42(6), p. 703-9.

4 Etzioni D. A., Mack T. M., Beart R. W., and Kaiser A. M., 2009, "Diverticulitis in the United States: 1998-2005: changing patterns of disease and treatment", Ann Surg, 249(2), p. 210-7.

5 Draaisma W. A., van de Wall B. J., Vermeulen J., Unlu C., de Korte N., and Swank H. A., 2009, "[Treatment for diverticulitis not thoroughly researched]", Ned Tijdschr Geneeskd, 153, p. A648.

6 "KiwaPrismant", KiwaPrismant, www.kiwaprismant.nl.

7 Ambrosetti P., Robert J. H., Witzig J. A., Mirescu D., Mathey P., Borst F., and Rohner A., 1994, "Acute left colonic diverticulitis in young patients", J Am Coll Surg, 179(2), p. 156-60.

8 Schauer P. R., Ramos R., Ghiatas A. A., and Sirinek K. R., 1992, "Virulent diverticular disease in young obese men", Am J Surg, 164(5), p. 443-6; discussion 446-8.

9 Lahat A., Menachem Y., Avidan B., Yanai H., Sakhnini E., Bardan E., and Bar-Meir S., 2006, "Diverticulitis in the young patient--is it different ?", World J Gastroenterol, 12(18), p. 2932-5.

10 Acosta J. A., Grebenc M. L., Doberneck R. C., McCarthy J. D., and Fry D. E., 1992, "Colonic diverticular disease in patients 40 years old or younger", Am Surg, 58(10), p. 605-7.

11 Rodkey G. V., and Welch C. E., 1984, "Changing patterns in the surgical treatment of diverticular disease", Ann Surg, 200(4), p. 466-78.

12 Hinchey E. J., Schaal P. G., and Richards G. K., 1978, "Treatment of perforated diverticular disease of the colon", Adv Surg, 12, p. 85-109.

13 Wasvary H., Turfah F., Kadro O., and Beauregard W., 1999, "Same hospitalization resection for acute diverticulitis", Am Surg, 65(7), p. 632-5; discussion 636.

14 Klarenbeek B. R., de Korte N., van der Peet D. L., and Cuesta M. A., 2011, "Review of current classifications for diverticular disease and a translation into clinical practice", Int J Colorectal Dis.

15 Kaiser A. M., Jiang J. K., Lake J. P., Ault G., Artinyan A., Gonzalez-Ruiz C., Essani R., and Beart R. W., 2005, "The management of complicated diverticulitis and the role of computed tomography", Am J Gastroenterol, 100(4), p. 910-7.

16 Ambrosetti P., Becker C., and Terrier F., 2002, "Colonic diverticulitis: impact of imaging on surgical management -- a prospective study of 542 patients", Eur Radiol, 12(5), p. 1145-9.

17 Stollman N. H., and Raskin J. B., 1999, "Diagnosis and management of diverticular disease of the colon in adults. Ad Hoc Practice Parameters Committee of the American College of Gastroenterology", Am J Gastroenterol, 94(11), p. 3110-21.

18 Broderick-Villa G., Burchette R. J., Collins J. C., Abbas M. A., and Haigh P. I., 2005, "Hospitalization for acute diverticulitis does not mandate routine elective colectomy", Arch Surg, 140(6), p. 576-81; discussion 581-3.

19 Mäkelä J., Vuolio S., Kiviniemi H., and Laitinen S., 1998, "Natural history of diverticular disease: when to operate?", Dis Colon Rectum, 41(12), p. 1523-8.
20 Anaya D. A., and Flum D. R., 2005, "Risk of emergency colectomy and colostomy in patients with diverticular disease", Arch Surg, 140(7), p. 681-5.
21 Haglund U., Hellberg R., Johnsén C., and Hultén L., 1979, "Complicated diverticular disease of the sigmoid colon. An analysis of short and long term outcome in 392 patients", Ann Chir Gynaecol, 68(2), p. 41-6.
22 Larson D. M., Masters S. S., and Spiro H. M., 1976, "Medical and surgical therapy in diverticular disease: a comparative study", Gastroenterology, 71(5), p. 734-7.
23 Parks T. G., 1969, "Natural history of diverticular disease of the colon. A review of 521 cases", Br Med J, 4(5684), p. 639-42.
24 Ambrosetti P., Grossholz M., Becker C., Terrier F., and Morel P., 1997, "Computed tomography in acute left colonic diverticulitis", Br J Surg, 84(4), p. 532-4.
25 Biondo S., Parés D., Martí Ragué J., Kreisler E., Fraccalvieri D., and Jaurrieta E., 2002, "Acute colonic diverticulitis in patients under 50 years of age", Br J Surg, 89(9), p. 1137-41.
26 Chapman J. R., Dozois E. J., Wolff B. G., Gullerud R. E., and Larson D. R., 2006, "Diverticulitis: a progressive disease? Do multiple recurrences predict less favorable outcomes?", Ann Surg, 243(6), p. 876-830; discussion 880-3.
27 Nylamo E., 1990, "Diverticulitis of the colon: role of surgery in preventing complications", Ann Chir Gynaecol, 79(3), p. 139-42.
28 Lorimer J. W., 1997, "Is prophylactic resection valid as an indication for elective surgery in diverticular disease?", Can J Surg, 40(6), p. 445-8.
29 Somasekar K., Foster M. E., and Haray P. N., 2002, "The natural history diverticular disease: is there a role for elective colectomy?", J R Coll Surg Edinb, 47(2), p. 481-2, 484.
30 Andeweg C., Peters J., Bleichrodt R., and van Goor H., 2008, "Incidence and risk factors of recurrence after surgery for pathology-proven diverticular disease", World J Surg, 32(7), p. 1501-6.
31 Hart A. R., Kennedy H. J., Stebbings W. S., and Day N. E., 2000, "How frequently do large bowel diverticula perforate? An incidence and cross-sectional study", Eur J Gastroenterol Hepatol, 12(6), p. 661-5.
32 Pittet O., Kotzampassakis N., Schmidt S., Denys A., Demartines N., and Calmes J. M., 2009, "Recurrent left colonic diverticulitis episodes: more severe than the initial diverticulitis?", World J Surg, 33(3), p. 547-52.
33 Klarenbeek B. R., Samuels M., van der Wal M. A., van der Peet D. L., Meijerink W. J., and Cuesta M. A., 2010, "Indications for elective sigmoid resection in diverticular disease", Ann Surg, 251(4), p. 670-4.
34 Schweitzer J., Casillas R. A., and Collins J. C., 2002, "Acute diverticulitis in the young adult is not "virulent."", Am Surg, 68(12), p. 1044-7.
35 Guzzo J., and Hyman N., 2004, "Diverticulitis in young patients: is resection after a single attack always warranted?", Dis Colon Rectum, 47(7), p. 1187-90; discussion 1190-1.
36 Ouriel K., and Schwartz S. I., 1983, "Diverticular disease in the young patient", Surg Gynecol Obstet, 156(1), p. 1-5.
37 Freischlag J., Bennion R. S., and Thompson J. E., 1986, "Complications of diverticular disease of the colon in young people", Dis Colon Rectum, 29(10), p. 639-43.

38 Rothenberger D. A., and Wiltz O., 1993, "Surgery for complicated diverticulitis", Surg Clin North Am, 73(5), p. 975-92.
39 Nelson R. S., Velasco A., and Mukesh B. N., 2006, "Management of diverticulitis in younger patients", Dis Colon Rectum, 49(9), p. 1341-5.
40 Janes S., Meagher A., Faragher I. G., Shedda S., and Frizelle F. A., 2009, "The place of elective surgery following acute diverticulitis in young patients: when is surgery indicated? An analysis of the literature", Dis Colon Rectum, 52(5), p. 1008-16.
41 Helderman J. H., and Goral S., 2002, "Gastrointestinal complications of transplant immunosuppression", J Am Soc Nephrol, 13(1), p. 277-87.
42 Hwang S. S., Cannom R. R., Abbas M. A., and Etzioni D., 2010, "Diverticulitis in transplant patients and patients on chronic corticosteroid therapy: a systematic review", Dis Colon Rectum, 53(12), p. 1699-707.
43 Dalla Valle R., Capocasale E., Mazzoni M. P., Busi N., Benozzi L., Sivelli R., and Sianesi M., 2005, "Acute diverticulitis with colon perforation in renal transplantation", Transplant Proc, 37(6), p. 2507-10.
44 Qasabian R. A., Meagher A. P., Lee R., Dore G. J., and Keogh A., 2004, "Severe diverticulitis after heart, lung, and heart-lung transplantation", J Heart Lung Transplant, 23(7), p. 845-9.
45 Lederman E. D., Conti D. J., Lempert N., Singh T. P., and Lee E. C., 1998, "Complicated diverticulitis following renal transplantation", Dis Colon Rectum, 41(5), p. 613-8.
46 McCune T. R., Nylander W. A., Van Buren D. H., Richie R. E., MacDonell R. C., Johnson H. K., Shull H., Cate C. K., and Helderman J. H., 1992, "Colonic screening prior to renal transplantation and its impact on post-transplant colonic complications", Clin Transplant, 6(2), p. 91-6.
47 Sachar D. B., and NDSG, 2008, "Diverticulitis in immunosuppressed patients", J Clin Gastroenterol, 42(10), p. 1154-5.
48 Lorimer J. W., and Doumit G., 2007, "Comorbidity is a major determinant of severity in acute diverticulitis", Am J Surg, 193(6), p. 681-5.
49 Sorser S. A., Hazan T. B., Piper M., and Maas L. C., 2009, "Obesity and complicated diverticular disease: is there an association?", South Med J, 102(4), p. 350-3.
50 Zaidi E., and Daly B., 2006, "CT and clinical features of acute diverticulitis in an urban U.S. population: rising frequency in young, obese adults", AJR Am J Roentgenol, 187(3), p. 689-94.
51 Dobbins C., Defontgalland D., Duthie G., and Wattchow D. A., 2006, "The relationship of obesity to the complications of diverticular disease", Colorectal Dis, 8(1), p. 37-40.
52 Aldoori W., and Ryan-Harshman M., 2002, "Preventing diverticular disease. Review of recent evidence on high-fibre diets", Can Fam Physician, 48, p. 1632-7.
53 Aldoori W. H., Giovannucci E. L., Rimm E. B., Wing A. L., Trichopoulos D. V., and Willett W. C., 1994, "A prospective study of diet and the risk of symptomatic diverticular disease in men", Am J Clin Nutr, 60(5), p. 757-64.
54 Andeweg C. S., Knobben L., Hendriks J. C., Bleichrodt R. P., and van Goor H., 2011, "How to Diagnose Acute Left-sided Colonic Diverticulitis: Proposal for a Clinical Scoring System", Ann Surg, 253(5), p. 940-6.
55 Laméris W., van Randen A., van Gulik T. M., Busch O. R., Winkelhagen J., Bossuyt P. M., Stoker J., and Boermeester M. A., 2010, "A clinical decision rule to establish the diagnosis of acute diverticulitis at the

emergency department", Dis Colon Rectum, 53(6), p. 896-904.

56 Laurell H., Hansson L. E., and Gunnarsson U., 2007, "Acute diverticulitis--clinical presentation and differential diagnostics", Colorectal Dis, 9(6), p. 496-501; discussion 501-2.

57 Toorenvliet B. R., Bakker R. F., Breslau P. J., Merkus J. W., and Hamming J. F., 2010, "Colonic diverticulitis: a prospective analysis of diagnostic accuracy and clinical decision-making", Colorectal Dis, 12(3), p. 179-86.

58 Cho K. C., Morehouse H. T., Alterman D. D., and Thornhill B. A., 1990, "Sigmoid diverticulitis: diagnostic role of CT--comparison with barium enema studies", Radiology, 176(1), p. 111-5.

59 Ambrosetti P., Jenny A., Becker C., Terrier T. F., and Morel P., 2000, "Acute left colonic diverticulitis--compared performance of computed tomography and water-soluble contrast enema: prospective evaluation of 420 patients", Dis Colon Rectum, 43(10), p. 1363-7.

60 Stoker J., van Randen A., Laméris W., and Boermeester M. A., 2009, "Imaging patients with acute abdominal pain", Radiology, 253(1), p. 31-46.

61 Ambrosetti P., 2008, "Acute diverticulitis of the left colon: value of the initial CT and timing of elective colectomy", J Gastrointest Surg, 12(8), p. 1318-20.

62 Balfe D. M., Levine M. S., Ralls P. W., Bree R. L., DiSantis D. J., Glick S. N., Megibow A. J., Saini S., Shuman W. P., Greene F. L., Laine L. A., and Lillemoe K., 2000, "Evaluation of left lower quadrant pain. American College of Radiology. ACR Appropriateness Criteria", Radiology, 215 Suppl, p. 167-71.

63 Laméris W., van Randen A., Bipat S., Bossuyt P. M., Boermeester M. A., and Stoker J., 2008, "Graded compression ultrasonography and computed tomography in acute colonic diverticulitis: meta-analysis of test accuracy", Eur Radiol, 18(11), p. 2498-511.

64 Liljegren G., Chabok A., Wickbom M., Smedh K., and Nilsson K., 2007, "Acute colonic diverticulitis: a systematic review of diagnostic accuracy", Colorectal Dis, 9(6), p. 480-8.

65 Laméris W., van Randen A., van Es H. W., van Heesewijk J. P., van Ramshorst B., Bouma W. H., ten Hove W., van Leeuwen M. S., van Keulen E. M., Dijkgraaf M. G., Bossuyt P. M., Boermeester M. A., Stoker J., and OPTIMA study group, 2009, "Imaging strategies for detection of urgent conditions in patients with acute abdominal pain: diagnostic accuracy study", BMJ, 338, p. b2431.

66 Van Randen A., Laméris W., van Es H. W., van Heesewijk H. P., van Ramshorst B., Ten Hove W., Bouma W. H., van Leeuwen M. S., van Keulen E. M., Bossuyt P. M., Stoker J., Boermeester M. A., and on behalf of the OPTIMA study group, 2011, "A comparison of the Accuracy of Ultrasound and Computed Tomography in common diagnoses causing acute abdominal pain", Eur Radiol, 21(7), p. 1535-1545.

67 Heverhagen J. T., Sitter H., Zielke A., and Klose K. J., 2008, "Prospective evaluation of the value of magnetic resonance imaging in suspected acute sigmoid diverticulitis", Dis Colon Rectum, 51(12), p. 1810-5.

68 Halpenny D. F., McNeil G., Snow A., Geoghegan T., and Torreggiani W. C., 2009, "Prospective evaluation of the value of magnetic resonance imaging in suspected acute sigmoid diverticulitis", Dis Colon Rectum, 52(5), p. 1030-1; author reply 1031.

69 Ajaj W., Ruehm S. G., Lauenstein T., Goehde S., Kuehle C., Herborn C. U., Langhorst J.,

Zoepf T., Gerken G., and Goyen M., 2005, "Dark-lumen magnetic resonance colonography in patients with suspected sigmoid diverticulitis: a feasibility study", Eur Radiol, 15(11), p. 2316-22.

70 Schreyer A. G., Fürst A., Agha A., Kikinis R., Scheibl K., Schölmerich J., Feuerbach S., Herfarth H., and Seitz J., 2004, "Magnetic resonance imaging based colonography for diagnosis and assessment of diverticulosis and diverticulitis", Int J Colorectal Dis, 19(5), p. 474-80.

71 Lahat A., Yanai H., Menachem Y., Avidan B., and Bar-Meir S., 2007, "The feasibility and risk of early colonoscopy in acute diverticulitis: a prospective controlled study", Endoscopy, 39(6), p. 521-4.

72 Sakhnini E., Lahat A., Melzer E., Apter S., Simon C., Natour M., Bardan E., and Bar-Meir S., 2004, "Early colonoscopy in patients with acute diverticulitis: results of a prospective pilot study", Endoscopy, 36(6), p. 504-7.

73 Hale W. B., and NDSG, 2008, "Colonoscopy in the diagnosis and management of diverticular disease", J Clin Gastroenterol, 42(10), p. 1142-4.

74 Crispin A., Birkner B., Munte A., Nusko G., and Mansmann U., 2009, "Process quality and incidence of acute complications in a series of more than 230,000 outpatient colonoscopies", Endoscopy, 41(12), p. 1018-25.

75 Brayko C. M., Kozarek R. A., Sanowski R. A., and Howells T., 1984, "Diverticular rupture during colonoscopy. Fact or fancy?", Dig Dis Sci, 29(5), p. 427-31.

76 Krones C. J., Klinge U., Butz N., Junge K., Stumpf M., Rosch R., Hermanns B., Heussen N., and Schumpelick V., 2006, "The rare epidemiologic coincidence of diverticular disease and advanced colonic neoplasia", Int J Colorectal Dis, 21(1), p. 18-24.

77 Stefánsson T., Ekbom A., Sparèn P., and Påhlman L., 2004, "Association between sigmoid diverticulitis and left-sided colon cancer: a nested, population-based, case control study", Scand J Gastroenterol, 39(8), p. 743-7.

78 Meurs-Szojda M. M., Terhaar sive Droste J. S., Kuik D. J., Mulder C. J., and Felt-Bersma R. J., 2008, "Diverticulosis and diverticulitis form no risk for polyps and colorectal neoplasia in 4,241 colonoscopies", Int J Colorectal Dis, 23(10), p. 979-84.

79 Hjern F., Josephson T., Altman D., Holmström B., Mellgren A., Pollack J., and Johansson C., 2007, "Conservative treatment of acute colonic diverticulitis: are antibiotics always mandatory?", Scand J Gastroenterol, 42(1), p. 41-7.

80 Lahat A., Yanai H., Sakhnini E., Menachem Y., and Bar-Meir S., 2008, "Role of colonoscopy in patients with persistent acute diverticulitis", World J Gastroenterol, 14(17), p. 2763-6.

81 Alonso S., Pera M., Parés D., Pascual M., Gil M. J., Courtier R., and Grande L., 2010, "Outpatient treatment of patients with uncomplicated acute diverticulitis", Colorectal Dis, 12(10 Online), p. e278-82.

82 Al-Sahaf O., Al-Azawi D., Fauzi M. Z., El-Masry S., and Gillen P., 2008, "Early discharge policy of patients with acute colonic diverticulitis following initial CT scan", Int J Colorectal Dis, 23(8), p. 817-20.

83 Tursi A., Brandimarte G., Elisei W., Giorgetti G. M., Inchingolo C. D., Danese S., and Aiello F., 2008, "Assessment and grading of mucosal inflammation in colonic diverticular disease", J Clin Gastroenterol, 42(6), p. 699-703.

84 Schug-Pass C., Geers P., Hügel O., Lippert H., and Köckerling F., 2010, "Prospective randomized trial comparing short-term antibiotic therapy versus standard therapy for acute uncomplicated sigmoid diverticulitis", Int J Colorectal Dis, 25(6), p. 751-9.

85 Ribas Y., Bombardó J., Aguilar F., Jovell E., Alcantara-Moral M., Campillo F., Lleonart X., and Serra-Aracil X., 2010, "Prospective randomized clinical trial assessing the efficacy of a short course of intravenously administered amoxicillin plus clavulanic acid followed by oral antibiotic in patients with uncomplicated acute diverticulitis", Int J Colorectal Dis, 25(11), p. 1363-70.

86 Eglinton T., Nguyen T., Raniga S., Dixon L., Dobbs B., and Frizelle F. A., 2010, "Patterns of recurrence in patients with acute diverticulitis", Br J Surg, 97(6), p. 952-7.

87 "http://www.igz.nl Basisset kwaliteits indicatoren publieke gezondheidszorg", http://www.igz.nl Basisset kwaliteits indicatoren publieke gezondheidszorg.

88 Köhler L., Sauerland S., and Neugebauer E., 1999, "Diagnosis and treatment of diverticular disease: results of a consensus development conference. The Scientific Committee of the European Association for Endoscopic Surgery", Surg Endosc, 13(4), p. 430-6.

89 1999, "Surgical treatment of diverticulitis. Patient Care Committee of the Society for Surgery of the Alimentary Tract (SSAT)", J Gastrointest Surg, 3(2), p. 212-3.

90 Rafferty J., Shellito P., Hyman N. H., Buie W. D., and Standards Committee of American Society of Colon and Rectal Surgeons, 2006, "Practice parameters for sigmoid diverticulitis", Dis Colon Rectum, 49(7), p. 939-44.

91 "http://www.worldgastroenterology.org/diverticular-disease.html", http://www.worldgastroenterology.org/diverticular-disease.html.

92 Chabok A., Påhlman L., Hjern F., Haapaniemi S., Smedh K., and AVOD Study Group, 2012, "Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis", Br J Surg, 99(4), p. 532-9.

93 Ridgway P. F., Latif A., Shabbir J., Ofriokuma F., Hurley M. J., Evoy D., O'Mahony J. B., and Mealy K., 2009, "Randomized controlled trial of oral vs intravenous therapy for the clinically diagnosed acute uncomplicated diverticulitis", Colorectal Dis, 11(9), p. 941-6.

94 Wilson R. G., Smith A. N., and Macintyre I. M., 1990, "Complications of diverticular disease and non-steroidal anti-inflammatory drugs: a prospective study", Br J Surg, 77(10), p. 1103-4.

95 Morris C. R., Harvey I. M., Stebbings W. S., Speakman C. T., Kennedy H. J., and Hart A. R., 2003, "Anti-inflammatory drugs, analgesics and the risk of perforated colonic diverticular disease", Br J Surg, 90(10), p. 1267-72.

96 Goh H., and Bourne R., 2002, "Non-steroidal anti-inflammatory drugs and perforated diverticular disease: a case-control study", Ann R Coll Surg Engl, 84(2), p. 93-6.

97 Corder A., 1987, "Steroids, non-steroidal anti-inflammatory drugs, and serious septic complications of diverticular disease", Br Med J (Clin Res Ed), 295(6608), p. 1238.

98 Ranji S. R., Goldman L. E., Simel D. L., and Shojania K. G., 2006, "Do opiates affect the clinical

99 Manterola C., Vial M., Moraga J., and Astudillo P., 2011, "Analgesia in patients with acute abdominal pain", Cochrane Database Syst Rev, (1), p. CD005660.

100 Ambrosetti P., Chautems R., Soravia C., Peiris-Waser N., and Terrier F., 2005, "Long-term outcome of mesocolic and pelvic diverticular abscesses of the left colon: a prospective study of 73 cases", Dis Colon Rectum, 48(4), p. 787-91.

101 Hamy A., Paineau J., and Société de chirurgie viscérale de l'ouest (SCVO), 2001, "[Percutaneous drainage of perisigmoid abscesses of diverticular origin]", Ann Chir, 126(2), p. 133-7.

102 Brandt D., Gervaz P., Durmishi Y., Platon A., Morel P., and Poletti P. A., 2006, "Percutaneous CT scan-guided drainage vs. antibiotherapy alone for Hinchey II diverticulitis: a case-control study", Dis Colon Rectum, 49(10), p. 1533-8.

103 Siewert B., Tye G., Kruskal J., Sosna J., Opelka F., Raptopoulos V., and Goldberg S. N., 2006, "Impact of CT-guided drainage in the treatment of diverticular abscesses: size matters", AJR Am J Roentgenol, 186(3), p. 680-6.

104 Singh B., May K., Coltart I., Moore N. R., and Cunningham C., 2008, "The long-term results of percutaneous drainage of diverticular abscess", Ann R Coll Surg Engl, 90(4), p. 297-301.

105 Antolovic D., Reissfelder C., Koch M., Mertens B., Schmidt J., Büchler M. W., and Weitz J., 2009, "Surgical treatment of sigmoid diverticulitis--analysis of predictive risk factors for postoperative infections, surgical complications, and mortality", Int J Colorectal Dis, 24(5), p. 577-84.

106 Vermeulen J., Akkersdijk G. P., Gosselink M. P., Hop W. C., Mannaerts G. H., van der Harst E., Coene P. P., Weidema W. F., and Lange J. F., 2007, "Outcome after emergency surgery for acute perforated diverticulitis in 200 cases", Dig Surg, 24(5), p. 361-6.

107 Morris C. R., Harvey I. M., Stebbings W. S., and Hart A. R., 2008, "Incidence of perforated diverticulitis and risk factors for death in a UK population", Br J Surg, 95(7), p. 876-81.

108 Ricciardi R., Baxter N. N., Read T. E., Marcello P. W., Hall J., and Roberts P. L., 2009, "Is the decline in the surgical treatment for diverticulitis associated with an increase in complicated diverticulitis?", Dis Colon Rectum, 52(9), p. 1558-63.

109 Dellinger R. P., Levy M. M., Rhodes A., Annane D., Gerlach H., Opal S. M., Sevransky J. E., Sprung C. L., Douglas I. S., Jaeschke R., Osborn T. M., Nunnally M. E., Townsend S. R., Reinhart K., Kleinpell R. M., Angus D. C., Deutschman C. S., Machado F. R., Rubenfeld G. D., Webb S. A., Beale R. J., Vincent J. L., Moreno R., and Pediatric Subgroup, 2013, "Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012", Crit Care Med, 41(2), p. 580-637.

110 Rivers E., Nguyen B., Havstad S., Ressler J., Muzzin A., Knoblich B., Peterson E., Tomlanovich M., and Early Goal-Directed Therapy Collaborative Group, 2001, "Early goal-directed therapy in the treatment of severe sepsis and septic shock", N Engl J Med, 345(19), p. 1368-77.

111 Lin S. M., Huang C. D., Lin H. C., Liu C. Y., Wang C. H., and Kuo H. P., 2006, "A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial", Shock, 26(6), p. 551-7.

112 Vermeulen J., Coene P. P., Van Hout N. M., van der Harst E., Gosselink M. P., Mannaerts G. H., Weidema W. F., and Lange J. F., 2009, "Restoration of bowel continuity after surgery for acute perforated diverticulitis: should Hartmann's procedure be considered

a one-stage procedure?", Colorectal Dis, 11(6), p. 619-24.
113 Salem L., Veenstra D. L., Sullivan S. D., and Flum D. R., 2004, "The timing of elective colectomy in diverticulitis: a decision analysis", J Am Coll Surg, 199(6), p. 904-12.
114 Kam M. H., Tang C. L., Chan E., Lim J. F., and Eu K. W., 2009, "Systematic review of intraoperative colonic irrigation vs. manual decompression in obstructed left-sided colorectal emergencies", Int J Colorectal Dis, 24(9), p. 1031-7.
115 Abbas S., 2007, "Resection and primary anastomosis in acute complicated diverticulitis, a systematic review of the literature", Int J Colorectal Dis, 22(4), p. 351-7.
116 Constantinides V. A., Heriot A., Remzi F., Darzi A., Senapati A., Fazio V. W., and Tekkis P. P., 2007, "Operative strategies for diverticular peritonitis: a decision analysis between primary resection and anastomosis versus Hartmann's procedures", Ann Surg, 245(1), p. 94-103.
117 Vermeulen J., and Lange J. F., 2010, "Treatment of perforated diverticulitis with generalized peritonitis: past, present, and future", World J Surg, 34(3), p. 587-93.
118 Alamili M., Gögenur I., and Rosenberg J., 2009, "Acute complicated diverticulitis managed by laparoscopic lavage", Dis Colon Rectum, 52(7), p. 1345-9.
119 Swank H., Vermeulen J., Lange JF., 2010, " The ladies trial: laparoscopic peritoneal lavage or resection for purulent peritonitis and Hartmann's procedure or resection with primary anastomosis for purulent or faecal peritonitis in perforated diverticulitis", BMC Surg, 29 (10).
120 Wong W. D., Wexner S. D., Lowry A., Vernava A., Burnstein M., Denstman F., Fazio V., Kerner B., Moore R., Oliver G., Peters W., Ross T., Senatore P., and Simmang C., 2000, "Practice parameters for the treatment of sigmoid diverticulitis--supporting documentation. The Standards Task Force. The American Society of Colon and Rectal Surgeons", Dis Colon Rectum, 43(3), p. 290-7.
121 Janes S., Meagher A., and Frizelle F. A., 2005, "Elective surgery after acute diverticulitis", Br J Surg, 92(2), p. 133-42.
122 Collins D., and Winter D. C., 2008, "Elective resection for diverticular disease: an evidence-based review", World J Surg, 32(11), p. 2429-33.
123 Richards R. J., and Hammitt J. K., 2002, "Timing of prophylactic surgery in prevention of diverticulitis recurrence: a cost-effectiveness analysis", Dig Dis Sci, 47(9), p. 1903-8.
124 Simpson J., Neal K. R., Scholefield J. H., and Spiller R. C., 2003, "Patterns of pain in diverticular disease and the influence of acute diverticulitis", Eur J Gastroenterol Hepatol, 15(9), p. 1005-10.
125 Klarenbeek B. R., Veenhof A. A., Bergamaschi R., van der Peet D. L., van den Broek W. T., de Lange E. S., Bemelman W. A., Heres P., Lacy A. M., Engel A. F., and Cuesta M. A., 2009, "Laparoscopic sigmoid resection for diverticulitis decreases major morbidity rates: a randomized control trial: short-term results of the Sigma Trial", Ann Surg, 249(1), p. 39-44.
126 Gervaz P., Inan I., Perneger T., Schiffer E., and Morel P., 2010, "A prospective, randomized, single-blind comparison of laparoscopic versus open sigmoid colectomy for diverticulitis", Ann Surg, 252(1), p. 3-8.
127 Siddiqui M. R., Sajid M. S., Qureshi S., Cheek E., and Baig M. K., 2010, "Elective laparoscopic sigmoid resection for diverticular disease has fewer complications

than conventional surgery: a meta-analysis", Am J Surg, 200(1), p. 144-61.

128 Purkayastha S., Constantinides V. A., Tekkis P. P., Athanasiou T., Aziz O., Tilney H., Darzi A. W., and Heriot A. G., 2006, "Laparoscopic vs. open surgery for diverticular disease: a meta-analysis of nonrandomized studies", Dis Colon Rectum, 49(4), p. 446-63.

129 Siddiqui M. R., Sajid M. S., Khatri K., Cheek E., and Baig M. K., 2010, "Elective open versus laparoscopic sigmoid colectomy for diverticular disease: a meta-analysis with the Sigma trial", World J Surg, 34(12), p. 2883-901.

130 Nygren J., Soop M., Thorell A., Hausel J., Ljungqvist O., and ERAS Group, 2009, "An enhanced-recovery protocol improves outcome after colorectal resection already during the first year: a single-center experience in 168 consecutive patients", Dis Colon Rectum, 52(5), p. 978-85.

131 Thaler K., Weiss E. G., Nogueras J. J., Arnaud J. P., Wexner S. D., and Bergamaschi R., 2003, "Recurrence rates at minimum 5-year follow-up: laparoscopic versus open sigmoid resection for uncomplicated diverticulitis", Surg Laparosc Endosc Percutan Tech, 13(5), p. 325-7.

132 Benn P. L., Wolff B. G., and Ilstrup D. M., 1986, "Level of anastomosis and recurrent colonic diverticulitis", Am J Surg, 151(2), p. 269-71.

133 Brodribb A. J., 1977, "Treatment of symptomatic diverticular disease with a high-fibre diet", Lancet, 1(8013), p. 664-6.

134 Ünlü C., Daniels L., Vrouenraets B. C., and Boermeester M. A., 2012, "A systematic review of high-fibre dietary therapy in diverticular disease", Int J Colorectal Dis, 27(4), p. 419-27.

135 Rafferty J., Shellito P., Hyman N. H., Buie W. D., and Standards Committee of American Society of Colon and Rectal Surgeons, 2006, "Practice parameters for sigmoid diverticulitis", Dis Colon Rectum, 49(7), p. 939-44.

136 Turunen P., Wikström H., Carpelan-Holmström M., Kairaluoma P., Kruuna O., and Scheinin T., 2010, "Smoking increases the incidence of complicated diverticular disease of the sigmoid colon", Scand J Surg, 99(1), p. 14-7.

137 Floch C. L., 2006, "Diagnosis and management of acute diverticulitis", J Clin Gastroenterol, 40 Suppl 3, p. S136-44.

138 Porta E., Germano A., Ferrieri A., and Koch M., 1994, "The natural history of diverticular disease of the colon: a role for antibiotics in preventing complications? A retrospective study", Riv Eur Sci Med Farmacol, 16(1-2), p. 33-9.

139 Tursi A., Brandimarte G., and Daffinà R., 2002, "Long-term treatment with mesalazine and rifaximin versus rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon", Dig Liver Dis, 34(7), p. 510-5.

140 Tursi A., 2007, "New physiopathological and therapeutic approaches to diverticular disease of the colon", Expert Opin Pharmacother, 8(3), p. 299-307.

141 Dughera L., Serra A. M., Battaglia E., Tibaudi D., Navino M., and Emanuelli G., 2004, "Acute recurrent diverticulitis is prevented by oral administration of a polybacterial lysate suspension", Minerva Gastroenterol Dietol, 50(2), p. 149-53.

Appendix 1

Search strategies for the relevant key words

Last search update February 2012

Subject: natural course of ACD
Date censoring: none
"Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "Natural history" [MesH] OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "Natural history" OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "uncomplicated"

Subject: natural course in young and immunocompromised patients
Date censoring: from 1960
Restrictions: none
"Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "Young" OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "Recurrence" [MesH] OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "diabetes mellitus" [MesH] OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "transplantation" [MesH] OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "immunosuppression" [MesH] OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "AIDS or HIV" [MesH] OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "neoplasms" [MesH]

Subject: colonoscopy
Date censoring: from 1970
Restrictions: none
"Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "colonoscopy" OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" ("Diverticulitis" OR "Diverticular disease") AND ("Colon carcinoma" OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "colon cancer" OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "IBD"

Subject: clinical diagnosis
Date censoring: from 1980
Restrictions: none
"Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND clinical parameters OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "sensitivity" OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] AND "diagnosis"

Subject: radiological imaging
Date censoring: from 1980
Restrictions: none
"Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "contrast enema" OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "Ultrasonography" [MeSH] OR "ultrasonography"[subheading] OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "Tomography, Spiral Computed" [MeSH] OR "Tomography, X-Ray Computed" [MeSH] OR "Tomography Scanners, X-Ray Computed" [Mesh] OR Computed Tomographic" [Mesh] OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "Magnetic Resonance Imaging" [Mesh] OR "Colonography,

Subject: uncomplicated diverticulitis
Date censoring: from 1975
Restrictions: none
"Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "uncomplicated diverticulitis" OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents"[Pharmacological Action])) OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]"
(("diverticulitis" [MeSH Terms] OR "diverticulitis" [AllFields]) AND ("intestines" [MeSH Terms] OR "intestines" [All Fields] OR "bowel" [All Fields]) AND ("rest" [MeSH Terms] OR "rest" [All Fields])) OR (("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND ("bed rest" [MeSH Terms] OR ("bed" [All Fields] AND "rest" [All Fields]) OR "bed rest" [All Fields] OR "bedrest" [All Fields])) OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND (("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND ("overweight" [MeSH Terms] OR "overweight" [All Fields])) OR (("diverticulitis" [MeSHTerms] OR "diverticulitis" [All Fields]) AND BMI [All Fields]) OR (("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND adipositas [All Fields]) OR (("diverticulum" [MeSH Terms] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND adipositas [All Fields]) OR (("diverticulum" [MeSH Terms] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND BMI [All Fields]) OR (("diverticulum" [MeSH Terms] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND ("overweight" [MeSH Terms] OR "overweight" [All Fields]))

"Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND [Diet Therapy] OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND Vegetables OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND Fruit OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND Starvation OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND Laxatives

Subject: complicated diverticulitis
Date censoring: from 1990
Restrictions: Adults 19+, Series > 50 patients
"Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "Abscess" [Mesh:NoExp] OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND Hinchey III OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "Hinchey IV" OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND "Diverticulitis, Colonic/mortality"[Mesh] OR "Diverticulitis, Colonic" [Mesh] AND "Intestinal Perforation" [Mesh] OR "Diverticulitis" [MesH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]" AND laparoscopy

'diverticulitis'/exp OR diverticulitis:ab,ti OR 'diverticular disease':ab,ti) AND ('laparoscopy'/exp OR 'laparoscopic surgery'/exp OR 'laparoscope'/exp OR 'minimally invasive surgery'/exp OR laparoscop*:ab,ti OR laparascop*:ab,ti OR (minimal*:ab,ti AND adj:ab,ti AND invasive:ab,ti)) AND ('acute disease'/exp OR 'emergency'/exp OR acute:ab,ti OR emergenc*:ab,ti OR 'colon perforation'/exp OR (perforat*:ab,ti AND [1970-2011]/py)) "Diverticulitis, Colonic"[Mesh] AND "Recurrence" [Mesh] AND "Therapeutics" [Mesh]
database

Subject: prevention of recurrence and antibiotics
Dare censoring: from 1966
Restricitons: none
("Diverticulitis" AND "Recurrence" AND "Therapy") OR ("Diverticulum, Colon" [Mesh]) AND (("Diet Therapy" [Mesh]) OR ("Dietary Fiber" [Mesh])).

(("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND ("overweight" [MeSH Terms] OR "overweight" [All Fields])) OR (("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND BMI [All Fields]) OR (("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND adipositas [All Fields]) OR (("diverticulum" [MeSH Terms] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND adipositas [All Fields]) OR (("diverticulum" [MeSH Terms] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND BMI [All Fields]) OR (("diverticulum" [MeSH Terms] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND ("overweight" [MeSH Terms] OR "overweight" [All Fields]))

(("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND ("smoking" [MeSH Terms] OR "smoking" [All Fields]) (("diverticular disease" [MeSH Terms] OR "diverticular disease" [All Fields]) AND ("smoking" [MeSH Terms] OR "smoking" [All Fields])

(("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND ("exercise" [MeSH Terms] OR "exercise" [All Fields] OR ("physical" [All Fields] AND "exercise" [All Fields]) OR "physical exercise" [All Fields])) OR (("diverticulum" [MeSH Terms] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND ("exercise" [MeSH Terms] OR "exercise" [All Fields] OR ("physical" [All Fields] AND "exercise" [All Fields]) OR "physical exercise" [All Fields])) OR (("diverticulitis" [MeSH

Terms] OR “diverticulitis” [All Fields]) AND (“physical therapy modalities” [MeSH Terms] OR (“physical” [All Fields] AND “therapy” [All Fields] AND “modalities” [All Fields]) OR “physical therapy modalities” [All Fields] OR “physiotherapy” [All Fields])) OR ((“diverticulum” [MeSH Terms] OR “diverticulum” [All Fields] OR (“diverticular” [All Fields] AND “disease” [All Fields]) OR “diverticular disease” [All Fields]) AND (“physical therapy modalities” [MeSH Terms] OR (“physical” [All Fields] AND “therapy” [All Fields] AND “modalities” [All Fields]) OR “physical therapy modalities” [All Fields] OR “physiotherapy” [All Fields]))

Subject: Elective surgery
Date censoring: 1970
Restrictions: none

“Diverticulitis” [MesH] OR “Diverticulitis, Colonic” [MeSH] OR “diverticulitis” [All Fields]”
AND Elective sigmoid resection OR “Diverticulitis” [MesH] OR “Diverticulitis, Colonic” [MeSH] OR “diverticulitis” [All Fields]” AND “Elective colectomy” OR “Diverticulitis” [MesH] OR “Diverticulitis, Colonic” [MeSH] OR “diverticulitis” [All Fields]” OR “Surgery” AND “Diverticulitis” [MesH] OR “Diverticulitis, Colonic” [MeSH] OR “diverticulitis” [All Fields]” AND “laparoscopic colectomy” OR “Diverticulitis” [MesH] OR “Diverticulitis, Colonic” [MeSH] OR “diverticulitis” [All Fields]” AND “laparosc*”.

Chapter 10

Summary and future perspectives

Samenvatting en toekomstperspectief

Summary and future perspectives

The studies presented in this thesis focus on a systematic approach diagnosing acute colonic diverticulitis (ACD), treatment dilemmas particularly in recurrent diverticulitis, and patient reported outcomes and Quality of Life (QoL) after surgical or medical treatment. Evidence based guidelines of diagnostics and treatment of diverticulitis have been established.

Chapter 1 is the introductory chapter in which a description is given of the aetiology and epidemiology of diverticula and diverticulitis. The current diagnosis and treatment of diverticulitis is outlined. The chapter also includes the content and objectives of this thesis.

PART ONE - *Clinical decision making in ACD* (Chapter 2-5)
In the first part of the thesis difficulties in diagnosing acute colonic diverticulitis (ACD) are discussed. ACD is a frequent suspected diagnosis in patients presenting with acute abdominal pain.[1] It is a challenge to correctly identify patients with ACD, because numerous other acute abdominal conditions mimic its clinical picture. Clinical assessment alone for the diagnosis of diverticulitis has been reported as insufficiently precise.[2-5] A decision model and external validation of the model to improve diagnostic accuracy of the clinical diagnosis ACD is presented, along with a systematic review of the clinical evaluation and diagnostic modalities to develop an evidence-based approach in diagnosing ACD. In the last chapter of Part 1 the potential pitfalls in diagnosing right-sided diverticulitis are discussed.

In **Chapter 2** relevant data of patients who entered the emergency department with acute abdominal pain and suspected ACD were retrospectively retrieved from medical charts and analyzed for factors predicting ACD. Independent predictors for having ACD after multivariable logistic regression model were age older than 50 years, one or more previous episodes of ACD, localization of pain in the lower left abdomen both on history taking and physical examination, pain on movement, and a C-reactive protein level higher than 50mg/l. Vomiting was a negative independent predictor for having ACD. Based on these variables, a decision model was made that can predict the probability of ACD. The optimal sensitivity and specificity of the model was 75% and 84%, respectively. Important clinical consequence of using the model is that additional imaging can be omitted when the chance of having ACD is high based on the model. Patients with mild symptoms without imaging and treated in an outpatient setting and patients with an acute abdomen in whom immediate operation was performed, were not included in the study. Hence, the decision model cannot be used in general practice, or in patients with suspected complicated diverticulitis.

An external validation of our decision model was done and described in **Chapter 3**. The diagnostic value of the decision model was compared with the decision rule for the diagnosis of patients with diverticulitis, developed by the Department of Surgery of the Academic Medical Centre Amsterdam (AMC).[6] In a subanalysis of patients suspected of ACD in the OPTIMA study, independent variables were selected that could be of value in predicting ACD. In this study, the triad pain in the lower left abdomen on physical examination, the absence of vomiting and a CRP >50mg/l had a very high predictive value (positive predictive value 97%) for patients having ACD. Approximately 25% of the patients with diverticulitis were positive for the triad. In a quarter of patients with suspected ACD, the diagnosis could be solely based on this triad. The clinical applicability of both models was tested with external validation using a third independent cohort of patients with acute abdominal pain.[7] The predictive value of each variable in the decision model was compared with the predictive value of each variable in the two validation cohorts to gain insight in the variables with the best discriminatory power. Results of the external validation study showed that the positive predictive value of our decision model remained intact (range 89%-92%), but the diagnosis ACD could only be made in 1 out of every 5 patients with a greater than 90% certainty. A disadvantage of our model was that it could only differentiate between patients with ACD and another diagnosis but lacked the ability to determine the alternative diagnosis. Also, the model could not distinguish between moderately ill and critically ill patients. Taking these limitations into account the diagnosis ACD can still be made with a probability reaching certainty in 1 out of 5 patients with suspected uncomplicated diverticulitis in our model, similar to 1 out of 4 patients with the triad of the AMC group.

In **Chapter 4** the added value of imaging in the diagnostic work-up of patients suspected of ACD was described. To this purpose the medical literature regarding accuracy of the clinical evaluation and diagnostic modalities for patients with suspected ACD was systematically reviewed to develop an evidence-based approach diagnosing ACD. Taking into account that the overall quality of the studies that reported the diagnostic accuracy of the clinical diagnosis, a contrast enema and a MRI was moderate to poor, we concluded that two-thirds of the diagnosis of ACD could be made without imaging and based on clinical evaluation alone. The role of MRI was not clear in diagnosing ACD. Contrast enema was inferior to US and CT in terms of sensitivity and specificity and was considered an obsolete imaging technique to diagnose ACD. Studies describing diagnostic accuracy of US and CT were of good quality and could be included in a meta-analysis. US and CT were comparable in diagnosing diverticulitis and superior to other modalities. CT had the advantage of higher specificity and the ability to better identify alternative diagnoses. We concluded that the first step of the diagnostic process should be an estimation of the probability of ACD based on clinical evaluation. In case of questionable disease, an ultrasound examination should be performed. In case of an inconclusive or negative US, a CT scan is the next diagnostic step to reveal the diagnosis. This process was named the

step-up approach to diagnose ACD, similar to the approach in diagnosing acute appendicitis.

In **Chapter 5** differences were evaluated in the clinical course between right- and left-sided ACD in a Western population. Right-sided colonic diverticulitis (RCD) is common in Asia but rare in the Western world.[8] Critical analysis of our data led to the conclusion that RCD has a low incidence, behaves as a self-limiting disease and acts more benign than left-sided ACD in Western patients. The historical concept that RCD in Western patients is an aggressive disease seemed merely a reflection of the unfamiliarity with this disease in the Western world, inadequate diagnostic workup and decisions made in the operating room. Outcome of RCD seemed more determined by the aggressive management of the disease than the nature of the disease itself.

PART TWO – *Treatment strategies, Risk factors and Quality of Life (QoL) in recurrent diverticulitis* (Chapter 6-8)
The second part of the thesis describes various treatment strategies for patients with recurrent episodes of ACD and the effect of conservative or operative treatment on quality of life (QoL) and other patient reported outcomes (PROs). In this part also risk factors were determined for recurrence of diverticulitis after surgery for uncomplicated or complicated diverticulitis.

Generally accepted indications for elective sigmoid resection after diverticulitis are obstruction, fistula formation, or the suspicion of colonic cancer. Recurrent episodes of ACD are generally considered an indication of a partial colonic resection. A frequently used argument to justify elective colonic resection after recurrent episodes of ACD is an increased risk of serious complications with each recurrent episode. Elective resection may reduce the risk of (complicated) recurrent ACD and may be a solution for patients with persistent pain after an episode of ACD. Elective resection, however, is not without risks. Patients risk major morbidity, mortality and the chance of stoma formation while the risk of recurrent ACD still may exist. Furthermore, persistent abdominal complaints seem common after surgery. Whether or not to perform an elective sigmoid resection in patients with recurrent episodes of ACD is a therapeutic dilemma. In order to properly advise the individual patient with recurrent episodes of diverticulitis it seems crucial to differentiate between patients who are likely to benefit from prophylactic resection preventing complicated disease and chronic abdominal complaints and patients with recurrent episodes who have a benign course. The decision to recommend surgery probably is influenced by the age and medical condition of the patient, the frequency and severity of the attack(s), and whether there are persistent symptoms after the acute episode.[1]

Recently, new theories about similarities between diverticulitis and inflammatory bowel disease have been proposed and good results with medication are reported. The use of 5-

aminosalicylic acid in combination with a non-absorbable antibiotic reduced persistent abdominal symptoms in between recurrences, but has not proved yet to diminish the risk of recurrent diverticulitis.[9-12] The results of these new treatment options have not been incorporated in recent guidelines, but might play an important role in the decision whether or not to operate. In terms of the best strategy for patients with recurrent episodes of diverticulitis, we designed a state-transition Markov model in which different treatment strategies in patients with recurrent episodes of diverticulitis were compared with Quality of Life (QoL) as primary outcome measure in **Chapter 6**. Four competing strategies were formulated based on the current uncertainty of the optimal treatment strategy in patients with recurrent episodes of diverticulitis, i.e., colonic resection after two episodes of diverticulitis and colonic resection or medical or conservative treatment after the third episode of diverticulitis. The course of events of 1,000 patients after two episodes of ACD was simulated in the model and sensitivity analyses were performed to determine which variables, according to the ranges in literature, would affect outcome. We found that colonic resection after two episodes of diverticulitis resulted in the lowest QALYs. The low QALYs associated with colonic resection after two episodes of diverticulitis were mainly caused by an early mortality risk related to the surgical procedure. Based on these results surgical treatment after two episodes of diverticulitis should no longer be advised. In patients suffering from a third episode of diverticulitis, the surgical, medical and conservative treatment strategies are similar in terms of quality-adjusted survival. Sensitivity analyses further revealed that surgical resection and conservative or medical treatment after the third episode of diverticulitis are superior to surgical resection after two episodes of diverticulitis. In the Markov model, patients with recurrent episodes of diverticulitis who received medical treatment generated the lowest QALYs compared to surgical and conservative treatment strategies because of the disutility associated with the use of chronic medication. An important finding was the relatively low incidence of persistent abdominal complaints compared to the other treatment strategies. Sensitivity analysis showed that if it is possible to reduce abdominal symptoms with 73%, medical treatment would become the treatment strategy of choice for patients with chronic abdominal pain in between recurrences, which percentage of reduction in symptoms has been described in previous studies.[13, 14] Results of the Markov analyses seriously questions surgery after two episodes of diverticulitis. Surgeons should not operate at quite the rate they have been trained to think. Patients may be counseled in choosing elective surgery if the frequency and severity of their episodes or abdominal complaints is sufficient to justify the burden of surgery and after treatment for abdominal complaints with medical treatment has been offered.

Clinical trials evaluating medical treatments or health interventions increasingly incorporate self-reported measures from patients often referred to as patient reported outcomes (PROs). A PRO is “any report of the status of a patient’s health condition that comes directly from the patient without interpretation of the patient’s response by a clinician or anyone else”. Several recent initiatives have emphasized the need to use PROs

in the assessment of quality of care, reflecting the need to include PROs in the choice of treatment modality.[15] The impact of conservative and operative treatment in case of recurrent diverticulitis complaints on QoL and PROs was evaluated in **Chapter 7**. A systematic review and meta-analysis were conducted and outcome measures were extracted from the literature and analyzed. Eight PROs were defined and graded according to clinical relevance, as proposed by the GRADE working group in outcomes critical for decision-making, important for decision-making, and outcomes of limited importance. [16, 17] Gastrointestinal QoL (GIQLI) and general Qol (SF-36, EORTC, CGQL), measured by validated questionnaires, were graded as PROs critical for decision-making. Disability, defined as the lack of being able to perform activities of daily living, physical activities and return to work, was also graded as critical for decision-making. Chronic abdominal pain, faecal incontinence and patient satisfaction were graded as PROs important for decision-making. Chronic abdominal pain was defined as persistence of abdominal pain after three months follow-up. Outcomes of limited clinical relevance were: persistent bowel symptoms, (i.e., hypogastric pain or bloating, diarrhea, constipation, flatulence, fever, painful defecation, dyschesia, pain or intestinal dysfunction, rectal bleeding, loose or hard stools), and urogenital symptoms (i.e., impotency, ejaculation difficulties, diminished libido and urinary dysfunction). Patients treated with laparoscopic colonic resection reported better general quality of life in the SF-36 questionnaire compared to conservatively treated patients, but this difference could not be reproduced in head to head analysis of both treatment options. Patients treated by laparoscopic colonic resection reported less gastrointestinal symptoms compared to conservative treated patients, also in a head to head analysis. In this study we showed that elective laparoscopic colonic resection, more than conservative treatment, might benefit the quality of life and gastrointestinal symptoms of patients with diverticulitis. However, the quality and power of studies to support this finding is low. Therefore a re-evaluation of laparoscopic surgery and conservative treatment is justified in patients with recurrent episodes of diverticulitis regarding what patients report as most important denominator of treatment success. Especially for the young patient with low co-morbidity for whom bowel symptoms might have large social implications, elective surgery could be a valuable treatment option. Results of this study also indicate that clinical decision-making should move from one-size fits all guidelines on when to operate to a more individual approach assessing the operative risk and the potential gain in quality of life for the individual patient.

In **Chapter 8**, we studied the incidence and risk factors of recurrence, and overall morbidity and mortality in patients who underwent surgery for uncomplicated and complicated diverticulitis. Recurrent diverticulitis was seen in 9% of the patients and two thirds of the recurrences occurred within five years after the index operation. Young patients and patients with persisting abdominal complaints had a significantly higher risk of recurrent diverticulitis. No association between an index emergency procedure and subsequent recurrent disease could be found. Furthermore, no relation was found between type of anastomosis and length of specimen and recurrent diverticulitis. One of

five operated patients reported chronic abdominal pain that persisted after the operation. Results of our study and novel data at that time of publication on the natural history of diverticulitis showed that most perforations do not occur at recurrences, but at the first attack of diverticulitis.[18] This study adds further proof that surgical resection after two episodes of diverticulitis is not beneficiary in terms of preventing complicated disease and reducing the risk of emergency procedures.

PART THREE – *Summary of the Dutch Guideline* (Chapter 9) *and future perspectives* (Chapter 10)
The third part of the thesis consists of a summary of the Dutch Guideline "Diagnostics and treatment of acute diverticulitis of the colon" and future perspectives are described. **Chapter 9** is a review article based on the Dutch guideline. The guideline was inspired by the fact that ACD is a very common condition but is characterized by reports having generated low evidence data and by diagnosis and treatment primarily based on the doctors' personal preferences rather than evidence. The guideline is based on the most recent international literature and therefore generalizable to any other Western country. This review article summarizes all relevant topics concerning epidemiology, classification, diagnosis and treatment of diverticulitis and reports levels of evidence for the conclusions from the literature leading to final recommendations. In summary, the guideline states that the natural history of diverticulitis is mild and can be largely treated by conservative means. Younger patients do not have a more aggressive course of disease than older patients but do have a higher risk of recurrent disease, however, the absolute risk difference is relatively small. The combination of pain in the lower left abdomen on physical examination, the absence of vomiting and a CRP >50mg/l has a high positive predictive value for diverticulitis, with good arguments to omit additional imaging. A conditional CT, only after a negative or inconclusive ultrasound provides the best results in imaging for diagnosing ACD. There is no evidence for the routine administration of antibiotics in patients with a clinically mild and uncomplicated diverticulitis. Pericolic or pelvic abscesses can initially be treated with antibiotics, possibly in combination with percutaneous drainage. If this treatment fails surgical drainage is required. Patients with a perforated diverticulitis resulting in peritonitis should undergo an emergency operation. Patient related factors and not so much the number of previous episodes of diverticulitis should play the most important role in selecting patients who might benefit from elective sigmoid resection, as also discussed in Part two of this thesis.

Future perspectives (Chapter 10)
Diverticulitis is a common, morbid and costly condition with remaining diagnostic and therapeutic challenges. The results of the studies in this thesis provide data for a better understanding of "diverticular disease" and diverticulitis in particular, but also raise questions.

The first question regards the usability of a clinical scoring system avoiding potentially harmful diagnostics. Will we be able to rightfully withhold patients suspected of ACD from additional imaging to come to the correct diagnosis?

Based on results of the clinical decision model we can only withhold one out of five patients from additional imaging to diagnose ACD. This would mean that the majority of patients still need imaging. The challenge in minimizing imaging is to achieve a better understanding of the individual variables that contribute to the diagnosis of ACD, and to distinguish between uncomplicated and complicated diverticulitis based on clinical and/or laboratory parameters without compromising quality of care. Increase in knowledge of predictive clinical and laboratory variables would benefit both the individual patient and society avoiding unnecessary hospital admissions and reducing costs. To illustrate there is a dramatic rise in the number of hospitalizations for ACD in the Netherlands in the past years. Expenditures for the hospital admissions in the Netherlands already exceed EUR 80 million per year.[19] This rise in hospital admissions is also notable in other countries. A study from the United States also showed an increase in hospital admissions, with the greatest rise in young patients.[20] Since diverticulitis is a recurrent disease in approximately a quarter of the patients, and recurrences can be multiple, patients run the risk of having multiple CT scans for suspicion of diverticulitis. This will impose an impressive burden on costs associated with imaging and not to forget patients' risk of exposure to radiation and contrast nephropathy. Further validation of prediction models in different subsets of patients with diverticulitis (first, recurrent, uncomplicated, complicated, primary healthcare population, hospital population) is the next step to individualize the diagnostic process in diverticulitis and to delineate the role of additional imaging and necessity for institutional care. The exponential growth of possibilities in health monitoring, home biotechnology and information technology in the near future will probably contribute to patient's self-management of (recurrent) diverticulitis, reduction of avoidable hospitalizations and associated costs.[21]

One of the first steps at this moment in reducing patient's burden and risks and controlling the costs through a more efficient use of resources is the step-up approach to diagnose diverticulitis as discussed in this thesis. The step-up approach is a conditional strategy in which a CT scan is only made after inconclusive or negative ultrasound. The first step of the diagnostic process is an estimation of the probability of ACD based on clinical evaluation, and ideally of the chance of complicated disease. In case of questionable disease, an ultrasound examination is carried out. When the US is inconclusive or is negative for diverticulitis, a CT scan is performed to reveal the diagnosis. This step-up approach is appealing from a patient and cost standpoint, however, geographic differences in use of imaging modalities may hamper widespread use. In a review amongst colon-and rectal surgeons from the UK and USA, differences in the use of initial imaging techniques were clearly demonstrated.[22, 23] Less than 10% of the colon- and rectal surgeons in the USA chose ultrasound as the initial imaging technique. This is probably due

to the imminent risk of legal claims and the high prevalence of obesity in the USA. Obesity renders ultrasound less valuable as initial screening tool for ACD. In many parts of Europe, abdominal ultrasound is performed by radiologists or other hospital based specialists. With advancing technology and increased experience of primary care physicians and physician assistants with out of hospital ultrasound, patient's comfort may increase and costs even decrease further.[24]

Second important question is what role surgery has in recurrent diverticulitis or patients with chronic abdominal pain in between recurrences? The main indication for elective colonic resection in patients with recurrent colonic diverticulitis was to prevent an emergency operation. More and more, however, surgical intervention aims at reducing the burden of recurrent disease and persistent abdominal complaints.[25-28] For some patients persistent abdominal pain in between the overt flares of diverticulitis result into a more chronic illness known as symptomatic uncomplicated diverticular disease (SUDD). SUDD is a subtype of diverticular disease in which there are persistent abdominal symptoms attributed to diverticula in the absence of macroscopically overt colitis or diverticulitis.[29]

We concluded that elective colonic resection after two episodes of diverticulitis should no longer be advised. Since this conclusion was based on a Markov analytic model, results are affected by the validity of the data used in the analysis. Retrospective observational trials and epidemiologic studies accounted for nearly the entire evidence from which the data used in this study is derived. High quality multicenter randomized clinical trials assessing the optimal treatment strategy for patients with recurrent diverticulitis or persisting symptoms are needed to provide better evidence answering the question regarding the role of elective surgery. Currently a Dutch multicenter RCT is being conducted (DIRECT trial), in which patients presenting themselves with persisting abdominal complaints after an episode of diverticulitis and/or three or more recurrences within two years will be included and randomized between surgical resection or medical treatment. Patients randomized for conservative treatment are treated according to the current daily practice (antibiotics, analgetics and/or expectant management). Patients randomized for elective resection will undergo an elective resection of the affected colon segment, with health related quality of life as the primary outcome.[30] Results of this trial are expected in the summer of 2015. Despite the importance of this trial trying to delineate the role of elective surgery in diverticulitis in a well-defined patient population, individual patient management may benefit less from results of this trial, particularly young patients with low risk and old patients with high risk of surgery. As mentioned before risk profiling and prediction of treatment success at the individual level using bio-information technology should gain more attention when aiming at improvements in personalized health.

Although we tend towards a more conservative approach in patients with recurrent episode of diverticulitis, Chapter 7 revealed a potential benefit in laparoscopic surgery for

patients with recurrent diverticulitis. General quality of life and improvement in gastrointestinal symptoms was significantly improved after laparoscopic colonic resection as compared to conservative treatment. With evidence of a potential benefit, however based on a few high risk of bias studies, laparoscopic surgery should be further studied assessing HRQoL and PROs. Such studies also include undertaking Big Data research which prompts us to put more effort in diverticulitis registries comparable to colorectal cancer and hernia registries but with long term outcomes and PROs.

Third question is what outcomes should be used in diverticulitis research? Many papers focus on short-term treatment results and physician derived outcomes. Fortunately, health status and quality of life are increasingly recognized as important in determining treatment results in diverticulitis. Papers often use the terms “quality of life” (QoL), “health status”, “functional status”, “health-related quality of life” (HRQoL) and “well-being” interchangeably.[31] PROs in patients with diverticulitis are not well defined and a confounding factor is the mixture of patients with diverticular disease and those with irritable bowel syndrome in series.[29, 32] Guidance from the GRADE working group is relevant to optimize the utilization of PROs in systematic reviews. To improve reporting and to draw more meaningful conclusions for the individual patient from diverticulitis research we need to better define PROs. This process of defining research outcomes should include patients with recurrent episodes of diverticulitis and with persistent abdominal complaints. Patient participation in research design has shown surprising (for physicians) shifts in focus and relevant outcomes.[33] For example fatigue or disutility from chronic medication use are seldom taking in to account in studies, but might be of crucial importance in patients with recurrent diverticulitis. Outcome measures relevant to patients are best derived by compiling focus groups to establish patient reported outcome measures (PROMS) and patient reported experience measures (PREMS) with in-depth interviewing.[34] Not only are PROMS and PREMS important for assessing quality of care and for evaluating outcomes of specific interventions and clinical assessment, but also for decision support. If PROMS and PREMS are clearly defined and validated for patients with recurrent diverticulitis or persistent abdominal complaints, we are able to reduce costs by streamlining health care to only those treatments and techniques that improve outcome. In the end this will lead to better value of the healthcare system by patients with equal or lower costs.[34]

Fourth question is what pathophysiology underlines persistence of abdominal pain and gastrointestinal symptoms in between recurrences and after surgical resection? With a better understanding of pain patterns in patients with diverticulitis we might be able to better intervene with medical treatment, further reducing the number of patients in need for resectional therapy. Results of the Markov analysis revealed that with a reduction of 73% in symptoms, the optimal treatment strategy in case of recurrent diverticulitis is medical treatment with 5-ASA and a non-absorbable antibiotic. This large reduction in symptoms has been described in previous studies.[13, 14] Although persistent abdominal

symptoms are increasingly recognized as a paramount problem in post-diverticulitis patients, we are unable to adequately define these patients because of lack of uniform definition and large variety of persistent abdominal symptoms. Persistent abdominal symptoms may reflect preexistent visceral hypersensitivity.[35] Abdominal symptoms after surgery for example may be related to a shorter bowel (increased bowel movements), to a relative stenosis of the anastomosis (obstructive signs) or to the presence of a stoma (leakage).

Diverticular disease is often defined as an acute attack of diverticulitis in a period of 'clinical silence', but this is not applicable to everyone. Some patients have long-standing pain, discomfort, or IBS symptoms resembling a chronic bowel disorder.[29] The possibility of chronic diverticular disease has recently received attention and a relation with altered gut microbiota and low-grade chronic inflammation has been hypothesized as cause of symptomatic diverticular disease and perhaps even as trigger for acute diverticulitis.[36] Alterations in the colonic microbiota interacting with host tissue may generate pain, disturbed bowel movements or recurrent diverticulitis.[37] Microbes in the human gastrointestinal tract contain 10^{12} to 10^{14} genes. The aggregate, multiorganismic, genetic code of those different microorganisms is referred to as the 'microbiome'.[38] Although the finding of altered microbiota in various disease states have been established, it is still unknown if these alterations cause the disease or are merely a consequence of the disease.[36] Research on the effects of microorganisms in diverticular disease is in its infancy; results are mainly derived from studies in other gastrointestinal diseases.[39] A recent Dutch study showed that the diagnosis diverticulitis can be made with relatively good accuracy based on microbiome analysis. The fecal microbiota diversity of patients with a first episode of acute uncomplicated diverticulitis significantly differed from control subjects, with the *Proteobacteria phylum* mainly determining this difference.[36] A significantly higher occurrence of *Bifidobacterium longum* and *Bifidobacterium animalis* was found in another series of patients with diverticulitis. Unfortunately this series was small (nine patients) and healthy controls were not included.[40] Establishing a causative role of gut microbiota in diverticular disease has great potential for disease prevention, diagnosis and treatment of disease and measuring therapy effect.[36]

The last question to be answered is how to disperse guidelines regarding diagnosis and treatment of ACD in the surgical and gastroenterological community? Contemporary data has shown that despite recent guidelines recommending a delay in elective colon resection beyond two episodes of uncomplicated diverticulitis, the incidence of elective colectomy substantially increased in the last two decades.[20, 41, 42] This can be partly explained by the lack of consensus regarding some topics between the different published guidelines and the often low quality of data. Very recently the evidence and consensus on diverticulitis in guidelines were systematically reviewed comparing all topics with recommendations.[43] Analyzing all six guidelines (the American Society of Colon and Rectal Surgeons 2006, the association of Coloproctology of Great Britain and Ireland 2011, the

Association of Surgeons of The Netherlands 2012, the Danish Surgical Society 2011, the European Association for Endoscopic Surgery and the World Society for Emergency Surgery 2013) there was only consensus with high quality data on the following:

- The need for imaging in addition to the clinical diagnosis
- The consideration to use rifaximin and probiotics before elective surgery
- Mild diverticulitis can be treated in an outpatient setting
- Elective surgery is not routine treatment
- When surgery is needed laparoscopic surgery in experienced hands is preferred
- For failed conservative treatment of abscesses and Hinchey III perforated diverticulitis laparoscopic lavage is a treatment option

Topics without consensus were the following:

- Optimal classification to stage the severity of diverticulitis
- Preferred imaging modality to diagnose diverticulitis
- Intraluminal imaging (colonoscopy) after an episode of diverticulitis
- Dietary restrictions and medical therapy
- Antibiotic treatment
- Surgical treatment for Hinchey III and IV perforated diverticulitis

We may conclude that based on current international guidelines many topics in diverticulitis did not reach consensus or reached consensus but without sufficient supporting evidence, which hampers dispersion of guidelines. To achieve broader consensus with regard to the management of acute diverticulitis and to address areas of debate an International Acute Diverticulitis Delphi study has been proposed recently by Professor Des Winter and co-workers. Results of this Delphi rounds are to be awaited.

This thesis had provided answers to important questions regarding diverticulitis and also raised questions for future research. In our opinion this research should focus on individual risk prediction for prognosis and treatment outcomes and outcomes relevant for the patient with diverticulitis.

Samenvatting en toekomstperspectief

Dit proefschrift "**Changing strategies in diverticulitis**" beschrijft een systematische aanpak voor het diagnosticeren van acute diverticulitis van het colon, therapeutische vraagstukken bij patiënten met recidiverende diverticulitis, en patiënt gerapporteerde uitkomstmaten en kwaliteit van leven na chirurgische of conservatieve behandeling van diverticulitis. Daarnaast wordt één hoofdstuk in dit proefschrift gewijd aan de richtlijn "Diagnostiek en behandeling van acute diverticulitis van het colon".

Hoofdstuk 1 is de inleiding van het proefschrift waarin een beschrijving van de ontstaanswijze en epidemiologie van diverticulosis coli en diverticulitis wordt beschreven. Daarnaast wordt de huidige diagnostiek en behandeling van acute diverticulitis uitgelegd. Dit hoofdstuk bevat tevens een overzicht van de hoofdstukken en doelstellingen van het proefschrift.

DEEL I – *Klinische besluitvorming in acute diverticulitis* (Hoofdstuk 2 t/m 5)
In het eerste deel van het proefschrift worden de huidige knelpunten en onvolkomenheden in het diagnosticeren van acute diverticulitis bediscussieerd. Diverticulitis is een veel voorkomende aandoening en komt vaak voor in de differentiaal diagnose bij patiënten die zich presenteren met acute buikpijn.[1] Het is een uitdaging om patiënten met diverticulitis juist te diagnosticeren, omdat er vele oorzaken voor pijn links onder in de buik kunnen zijn die op het beeld van acute diverticulitis lijken. Het stellen van de diagnose diverticulitis op basis van de klinische blik van de dokter leidt dan ook frequent tot een foutieve diagnose.[2-5] Om de diagnostische accuratesse van de anamnese, lichamelijk onderzoek en laboratorium parameters te verbeteren werd in dit proefschrift een klinisch beslismodel ontworpen. Externe validatie van dit beslismodel werd verricht in een tweetal andere cohorten van patiënten met diverticulitis. Ten slotte werd een systematische review verricht om tot een evidence-based advies te komen voor het diagnostische proces van patiënten met diverticulitis. In het laatste gedeelte van Deel I van het proefschrift worden de potentiële valkuilen in het diagnosticeren van rechtszijdige diverticulitis bediscussieerd.

In **Hoofdstuk 2** werden gegevens van patiënten die zich met acute buikpijn presenteerden op de SEH retrospectief verzameld en geanalyseerd. Gezocht werd naar individuele parameters in de anamnese, lichamelijk onderzoek en laboratorium parameters die voorspellend waren voor acute diverticulitis. Onafhankelijke voorspellende factoren voor het hebben van acute diverticulitis in het multivariabele logistische regressiemodel waren: leeftijd ouder dan 50 jaar, één of meerdere episodes van diverticulitis in de voorgeschiedenis, pijn links onder in de buik zowel anamnestisch als bij lichamelijk onderzoek, vervoerspijn, en een CRP waarde van meer dan 50mg/l. Braken was een negatief voorspellende waarde voor het hebben van diverticulitis. Op basis van deze variabelen werd een beslismodel gemaakt, dat de kans op het hebben van een diverticulitis bij

patiënten met acute buikpijn kan voorspellen. De optimale sensitiviteit en specificiteit van het model was respectievelijk 75% en 84%. Een belangrijke klinische consequentie van het model is dat bij een hoge kans op acute diverticulitis in het model, aanvullende beeldvormende diagnostiek achterwege kan worden gelaten. Patiënten met een milde diverticulitis die door de huisarts werden behandeld en patiënten met een acute buik die direct werden geopereerd werden niet geïncludeerd in deze studie. Dit betekent dat het klinische beslismodel niet gebruikt kan worden in de huisartsenpraktijk, of bij kritiek zieke patiënten die van gecompliceerde diverticulitis worden verdacht.

Externe validatie van het beslismodel werd verricht en beschreven in **Hoofdstuk 3**. De diagnostische waarde van het beslismodel werd vergeleken met een beslisregel voor de diagnose diverticulitis ontwikkeld door het Academisch Medisch Centrum in Amsterdam (AMC).[6] Vanuit een subanalyse van patiënten die verdacht werden van acute diverticulitis in de OPTIMA studie, werden onafhankelijke variabelen geselecteerd die van waarde konden zijn voor het diagnosticeren van acute diverticulitis. In deze studie was de trias pijn links onder in de buik bij lichamelijk onderzoek, de afwezigheid van braken en een CRP waarde van meer dan 50mg/l geassocieerd met een positief voorspellende waarde van 97% voor het hebben van diverticulitis. Van alle patiënten met diverticulitis had ongeveer 25% een positieve trias en kon de diagnose diverticulitis alleen op basis van de trias gesteld worden zonder aanvullende beeldvormende diagnostiek. Met behulp van externe validatie werd de klinische toepasbaarheid van beide modellen getest en gevalideerd met behulp van een derde onafhankelijk cohort met patiënten met acute buikpijn.[7] De positief voorspellende waarde van elke variabele in het beslismodel werd vergeleken met de positief voorspellende waarde van elke variabele in de twee validatie-cohorten, om zo inzicht te krijgen in het discriminerende vermogen van de verschillende variabelen. Resultaten van de externe validatie laten zien dat de positief voorspellende waarde van ons beslismodel intact bleef (range 89%-92%), en dat de diagnose diverticulitis in één op de vijf patiënten met meer dan 90% zekerheid gesteld kon worden. Een nadeel van ons beslismodel was dat het alleen kon differentiëren tussen de aan- en afwezigheid van diverticulitis, maar dat het de andere diagnose niet kon specificeren. Daarnaast kon het model ook niet discrimineren tussen matig zieke en kritiek zieke patiënten. Als men deze tekortkomingen van het model in acht neemt, dan kan met ons model in één op de vijf patiënten met aan zekerheid grenzende waarschijnlijkheid de diagnose diverticulitis zonder aanvullende beeldvorming gesteld worden, vergelijkbaar met één op de vier patiënten met de trias van de AMC studie groep.

In **Hoofdstuk 4** werd de additionele waarde van beeldvorming in het diagnostische proces van patiënten met de verdenking diverticulitis beschreven. Er werd een systematische review van de literatuur verricht aangaande de diagnostische accuratesse van de klinische diagnose en beeldvormende technieken, om zo tot een evidence-based advies te komen voor het diagnostische proces van patiënten met diverticulitis. Met inachtneming van de matig tot slechte kwaliteit van de studies die rapporteerden over de diagnostische

accuratesse van de klinische diagnose, colon inloop foto en MRI scan, konden we concluderen dat van tweederde van de patiënten met de verdenking diverticulitis, de diagnose gesteld kon worden op basis van alleen de klinische evaluatie en dat aanvullende beeldvorming achterwege gelaten kon worden. De rol van de MRI scan in het diagnosticeren van diverticulitis is nog niet duidelijk. De sensitiviteit en specificiteit van de colon inloop foto bleek inferieur ten opzichte van graded compression echografie en CT scan en wordt beschouwd als een obsolete techniek voor het diagnosticeren van diverticulitis. De studies die de diagnostische accuratesse van de echografie en de CT scan beschreven waren van goede kwaliteit en konden gebruikt worden voor meta-analyse. Graded compression echografie en CT waren vergelijkbaar in het diagnosticeren van diverticulitis en superieur ten opzichte van de andere beeldvormende technieken. CT had het voordeel van een betere specificiteit en kon beter een alternatieve diagnose identificeren. Wij concludeerden op basis van deze studie dat de eerste stap in het diagnostische proces van acute diverticulitis een schatting moet zijn van de kans op diverticulitis op basis van de klinische evaluatie, bijgestaan door de klinische beslis-modellen die voorhanden zijn. In geval van twijfel over de diagnose diverticulitis dient aanvullend een echografie verricht te worden. In het geval van een niet conclusieve of negatieve echografie, is een CT scan de volgende diagnostische stap om tot een diagnose te komen. Dit proces wordt de “step-up approach” genoemd, vergelijkbaar met het diagnostische proces van acute appendicitis.

In **Hoofdstuk 5** werden de verschillen tussen het klinische beloop van een rechtszijdige en linkszijdige diverticulitis vergeleken in een Westerse populatie. Rechtszijdige diverticulitis komt veel voor in Azië, maar minder vaak in de Westerse wereld.[8] Kritische analyse van onze data leidde tot de conclusie dat rechtszijdige diverticulitis een lage incidentie kent en veelal een zelf limiterend karakter heeft. Het historische concept dat rechtszijdige diverticulitis een agressiever beloop kent dan linkszijdige diverticulitis in de Westerse populatie lijkt vooral te zijn gebaseerd op aannames vanuit het verleden, toen de diagnose rechtszijdige diverticulitis door een inadequate diagnostische work-up veelal pas peroperatief werd gesteld. Door de invoering van routinematige beeldvorming van patiënten met acute buikpijn, heeft er een belangrijke verschuiving plaatsgevonden, waarbij rechtszijdige diverticulitis meer een radiologische dan een chirurgische diagnose is geworden.

DEEL II – *Behandelstrategieën, risicofactoren en kwaliteit van leven bij patiënten met recidiverende diverticulitis* (Hoofdstuk 6 t/m 8)
Het tweede deel van het proefschrift beschrijft de verschillende behandelstrategieën voor patiënten met recidiverende diverticulitis en het effect van conservatieve of operatieve behandeling van diverticulitis op kwaliteit van leven (KvL) en andere patiënt gerapporteer-de uitkomstmaten (patient reported outcomes – PROs). In dit deel van het proefschrift worden ook risicofactoren van een recidief diverticulitis na operatieve behandeling voor ongecompliceerde en gecompliceerde diverticulitis beschreven.

Algemeen geaccepteerde indicaties voor het ondergaan van een electieve sigmoid resectie na diverticulitis zijn obstructie, fistelvorming, of de verdenking van een maligniteit van het colon. Het hebben van recidiverende episodes van diverticulitis wordt ook beschouwd als een indicatie voor een sigmoid resectie. Het argument wat hier veelal voor gebruikt werd, was dat elke episode van diverticulitis het risico op een gecompliceerde diverticulitis vergrootte. Electieve sigmoidresectie kan de kans op een recidief diverticulitis, en daarmee ook de kans op een gecompliceerde diverticulitis verminderen, maar kan ook een oplossing zijn voor patiënten die persisterende pijnklachten houden na een episode van diverticulitis. Een electieve sigmoidresectie is echter niet geheel zonder risico. Patiënten riskeren de kans op morbiditeit, mortaliteit en de kans op een tijdelijk of permanent stoma, terwijl het risico op een recidief niet helemaal wordt weggenomen door een operatie. Bovendien kunnen er blijvende klachten van pijn optreden na een sigmoidresectie. Het wel of niet verrichten van een electieve sigmoidresectie in patiënten met recidiverende diverticulitis of peristerende pijn na een episode van diverticulitis blijft dan ook een therapeutisch dilemma. Om deze patiënten goed te adviseren, is het erg belangrijk patiënten te selecteren die waarschijnlijk hun voordeel doen bij een electieve sigmoidresectie om recidief (ongecompliceerde of gecompliceerde) diverticulitis en chronische abdominale pijnklachten te voorkomen en te behandelen. De beslissing om te opereren wordt beïnvloed door de leeftijd en de comorbiditeit van de patiënt, de ernst en de frequentie van de aanvallen en de aanwezigheid van persisterende pijnklachten.

Nieuwe theorieën over overeenkomsten tussen diverticulitis en inflammatoire darmaandoeningen hebben geleid tot nieuwe inzichten in de medicamenteuze behandeling van diverticulitis. Zo blijkt dat het gebruik van 5-aminosalicylic acid (5-ASA) in combinatie met een niet absorbeerbaar antibioticum, persisterende pijnklachten tussen episodes van diverticulitis kan doen verminderen. We hebben nog niet kunnen aantonen dat het gebruik van deze medicatie bij patiënten met diverticulitis ook kan leiden tot vermindering van het aantal recidieven.[9-12] De resultaten van medicamenteuze behandeling zijn nog niet opgenomen in recente richtlijnen, maar kunnen wellicht een belangrijke rol gaan spelen in de beslissing om wel of niet over te gaan tot een operatieve behandeling. Om de beste strategie te bepalen bij patiënten met recidiverende diverticulitis hebben wij een Markov model ontworpen waarin verschillende behandelstrategieën met elkaar werden vergeleken met KvL als primaire uitkomstmaat. Resultaten van dit Markov model zijn beschreven in **Hoofdstuk 6**. Er werden vier concurrerende strategieën met elkaar vergeleken, gebaseerd op de huidige onzekerheid over de optimale behandeling van patiënten met recidiverende diverticulitis. De vier strategieën waren sigmoidresectie na twee episodes van diverticulitis sigmoidresectie, medicamenteuze behandeling of conservatieve behandeling na drie episodes van diverticulitis. Het model simuleerde de verschillen tussen de vier strategieën en op basis van sensitiviteitsanalyses werd bepaald welke variabelen effect hadden op de uitkomsten van het model. We concludeerden dat het verrichten van een sigmoidresectie na twee episodes van diverticulitis resulteerde in de minste Quality Adjusted Life Years (QALYs). Dit werd met name veroorzaakt, doordat een electieve

sigmoidresectie een kans op mortaliteit kent. Een electieve resectie alleen op basis van twee episodes van diverticulitis moet dan ook niet langer geadviseerd worden aan patiënten. Na een derde episode van diverticulitis, waren chirurgische, medicamenteuze en conservatieve behandeling vergelijkbaar wat betreft QALYs. Patiënten die medicamenteus werden behandeld voor recidiverende diverticulitis genereerden de laagste QALYs, vanwege het ongemak dat wordt geassocieerd met chronisch medicatiegebruik. Een belangrijke bevinding bij de medicamenteus behandelde groep was echter de relatief lage incidentie van persisterende abdominale klachten. Sensitiviteitsanalyse liet zien dat medicamenteuze behandeling voor recidiverende diverticulitis de strategie van keus werd als de persisterende abdominale klachten met meer dan 73% konden worden gereduceerd. Dit percentage van symptoomreductie is beschreven in studies.[13, 14] Resultaten van de Markov analyse doen ernstig twijfelen aan het oude dogma dat na twee episodes van diverticulitis een sigmoidresectie geïndiceerd is. In de beslissing om te opereren moet de patiënt centraal staan. De patiënt moet, bijgestaan door de behandelend arts, uiteindelijk de afweging maken of de ernst en de frequentie van de klachten opwegen tegen de risico's van een chirurgische ingreep, maar pas nadat medicamenteuze behandeling is aangeboden aan de patiënt.

Klinische trials incorporeren in toenemende mate zelf gerapporteerde uitkomsten van patiënten als belangrijke uitkomstmaat, dit wordt ook wel patiënt gerelateerde uitkomsten in de Nederlandse literatuur, of patient related outcomes (PROs) in de Angelsaksische literatuur genoemd. Een PRO is gedefinieerd als elke uitkomst gerapporteerd door de patiënt, zonder tussenkomst of interpretatie van een arts of een willekeurige andere persoon. Veel recente initiatieven hebben opgeroepen in toenemende mate PROs te gaan gebruiken om de kwaliteit van onze zorg te meten, en PROs onderdeel te laten zijn in de keuze van een behandeling.[15] De impact van conservatieve of operatieve behandeling van recidiverende diverticulitis en persisterende klachten op de KvL en PROs werd geëvalueerd in **Hoofdstuk 7**. Een systematische review en meta-analyse werd verricht van de beschikbare literatuur over conservatieve en operatieve behandeling van diverticulitis, en relevante uitkomstmaten werden geselecteerd. In totaal werden acht PROs gedefinieerd en gerangschikt op basis van klinische relevantie, zoals voorgesteld door de GRADE working group. Klinische relevantie werd uitgedrukt in uitkomsten kritisch voor het nemen van een beslissing, belangrijk voor het nemen van een beslissing en uitkomsten met beperkte klinische relevantie.[16, 17] Gastrointestinale KvL (GIQLI) en algemene KvL (SF-36, EORTC, CGQL), gemeten met gevalideerde vragenlijsten, werden gerangschikt als PROs kritisch voor het nemen van een beslissing. Disability, gedefinieerd door het onvermogen om aan dagelijkse activiteiten en het arbeidsproces deel te nemen, werden eveneens als kritisch voor het nemen van een beslissing geduid. Chronische abdominale pijn, fecale incontinentie en patiënt tevredenheid werden gerangschikt als PROs belangrijk voor het nemen van een beslissing. Chronische abdominale pijn werd gedefinieerd als pijnklachten langer dan drie maanden. Uitkomsten met beperkte klinische relevantie waren: darmklachten (i.e., opgeblazen gevoel, diarree, obstipatie, winderigheid,

koorts, pijnlijke defecatie, dyschesia, rectaal bloedverlies) en urogenitale klachten (i.e., impotentie, moeizame ejaculatie, libidoverlies). Patiënten die een laparoscopische sigmoidresectie hadden ondergaan rapporteerden een betere algemene KvL in de SF-36 vragenlijst in vergelijking met de conservatief behandelde patiëntengroep, maar dit verschil kon niet worden teruggevonden in de studies die beide behandelmodaliteiten direct met elkaar vergeleken (head to head analysis). Patiënten die een laparoscopische sigmoidresectie hadden ondergaan rapporteerden minder gastrointestinale klachten in vergelijking met de conservatief behandelde groep, en dit verschil werd eveneens teruggevonden in de studies die beide behandelmodaliteiten direct met elkaar vergeleken. We concludeerden in deze studie dat electieve sigmoidresectie, meer dan conservatieve behandeling, is geassocieerd met een verbetering in de KvL en vermindering van de gastrointestinale klachten van patiënten met diverticulitis. Echter de kwaliteit en de power van de studies om deze conclusie te ondersteunen is laag. Een her-evaluatie van de rol van laparoscopische chirurgie of conservatieve behandeling van patiënten met een recidiverende diverticulitis lijkt noodzakelijk met als belangrijkste noemer voor een succesvolle behandeling patiëntgerapporteerde uitkomsten. Vooral voor de jonge patiënt met weinig comorbiditeit voor wie chronische gastrointestinale klachten veel sociale implicaties hebben, kan een chirurgische behandeling een waardevolle behandeloptie zijn. Resultaten van deze studie laten ook zien dat klinische besluitvorming vooral moet worden afgestemd op het individu en dat we af moeten stappen van one-size-fits-all richtlijnen over wel of niet opereren, maar per individuele patiënt het operatieve risico moeten afwegen tegen de potentiële winst in KvL.

In **Hoofdstuk 8** hebben we de incidentie en risicofactoren en morbiditeit en mortaliteit beschreven van patiënten die een electieve of acute sigmoidresectie ondergaan in verband met ongecompliceerde of gecompliceerde diverticulitis. Een recidief diverticulitis werd gezien bij 9% van de patiënten en bij twee derde van de patiënten ontstond het recidief binnen vijf jaar na de eerste operatie. Jonge patiënten en patiënten met persisterende abdominale klachten hadden significant meer risico op een recidief. Er kon geen relatie worden gevonden tussen het type operatie (electief of acuut), type anastomose en lengte van het preparaat en het ontstaan van een recidief. Eén op de vijf patiënten rapporteerde chronische abdominale pijn dat persisteerde na de resectie. Resultaten van deze studie en nieuw gepubliceerde data over het natuurlijk beloop van diverticulitis, ten tijde van publicatie van dit artikel, laten zien dat de meeste perforaties niet ontstaan bij een recidief diverticulitis, maar veelal een eerste presentatie zijn van de ziekte.[18]. Deze studie voegt meer bewijs toe aan het gegeven dat een chirurgische resectie na twee episodes van diverticulitis niet een gecompliceerd recidief, en daarmee een acute chirurgische interventie, voorkomt.

DEEL III – *Samenvatting van de Nederlandse Richtlijn* (Hoofdstuk 9) *en toekomst-perspectief* (Hoofdstuk 10)
Het derde deel van dit proefschrift is een samenvatting van de Nederlandse Richtlijn "Diagnostiek en behandeling van acute diverticulitis van het colon" en beschrijft het toekomstperspectief. **Hoofdstuk 9** is een review artikel gebaseerd op deze Nederlandse richtlijn. Het idee voor een richtlijn over diverticulitis was ontstaan door het feit dat acute diverticulitis een veel voorkomende aandoening is, maar dat wetenschappelijk onderzoek naar diverticulitis wordt gekenmerkt door veel studies van lage tot matige kwaliteit. Hierdoor is het diagnosticeren en behandelen van patiënten met diverticulitis vooral gebaseerd op voorkeur van de behandelend arts en niet zo zeer op evidence-based medicine. De richtlijn is gebaseerd op de meest recente internationale literatuur en is daarom toepasbaar in elk Westers land. Het review artikel is een samenvatting van alle relevante onderwerpen aangaande epidemiologie, classificatie, diagnose en behandeling van acute linkszijdige diverticulitis van het colon, en geeft conclusies over de mate van bewijskracht van de literatuur en aanbevelingen gebaseerd op deze conclusies.

De richtlijn concludeert dat het natuurlijk beloop van diverticulitis over het algemeen ongecompliceerd is en dat het overgrote deel van de patiënten met conservatieve maatregelen kan worden behandeld. Diverticulitis bij jonge patiënten behoeft geen andere behandeling dan bij oudere patiënten, maar kent wel een grotere recidiefkans. De grotere recidiefkans wordt vooral toegeschreven aan een groter "life-time"-risico op een recidief en niet aan een agressiever beloop van de ziekte. De combinatie van pijn links onder in de buik bij lichamelijk onderzoek, afwezigheid van braken en een CRP-waarde >50mg/l heeft een hoge voorspellende waarde voor de aanwezigheid van diverticulitis; beeldvormend onderzoek kan dan eventueel achterwege worden gelaten. Initieel echografie en alleen CT onderzoek als de uitslag van de echografie negatief of niet-conclusief is, geeft het beste resultaat bij beeldvormend onderzoek. Er is geen bewijs dat het routinematig toedienen van antibiotica bij patiënten met een ongecompliceerde diverticulitis effectief is. Een pericolisch of pelvien abces kan antibiotisch behandeld worden, eventueel in combinatie met een percutane drainage. Chirurgisch ingrijpen is alleen nodig indien deze behandeling faalt. Patiënten met een peritonitis ten gevolge van een geperforeerde diverticulitis dienen geopereerd te worden, maar er is discussie over de optimale chirurgische strategie. Patiëntgerelateerde factoren, en niet zo zeer het aantal recidieven, spelen de belangrijkste rol in de beslissing om wel of niet over te gaan tot een electieve sigmoidresectie, zoals ook bediscussieerd in Deel II van dit proefschrift.

Toekomstperspectief (Hoofdstuk 10)
Diverticulitis is een veelvoorkomende aandoening met nog veel onbeantwoorde diagnostische en therapeutische vraagstukken. In dit proefschrift wordt een deel van deze vraagstukken beantwoord, maar er worden ook nieuwe vraagstukken gegenereerd.

De eerste vraag die is ontstaan naar aanleiding van dit proefschrift is wat de bruikbaarheid van een klinisch scoresysteem is om daarmee het gebruik van potentieel schadelijke beeldvorming te kunnen verminderen. Zullen we in de toekomst beter in staat zijn om de diagnose diverticulitis te stellen zonder aanvullende beeldvorming? Ons klinische scoresysteem was bij één op de vijf patiënten in staat om de diagnose diverticulitis te stellen zonder aanvullende beeldvorming. Dit betekent dat bij het merendeel van de patiënten aanvullende beeldvorming noodzakelijk is om tot de juiste diagnose te komen. Om de diagnose diverticulitis te stellen zonder aanvullende beeldvorming, zullen we een beter begrip van de voorspellende waarde van de individuele klinische variabelen die bijdragen aan de diagnose diverticulitis moeten krijgen. Daarnaast moeten we beter het onderscheid kunnen maken tussen patiënten met ongecompliceerde en gecompliceerde diverticulitis op basis van klinische parameters zonder dat we daarmee de kwaliteit van zorg compromitteren. Een toename van de kennis van de voorspellende waarde van de klinische en laboratorium parameters in het diagnosticeren van diverticulitis kan leiden tot een vermindering van het aantal onnodige ziekenhuisopnames en daarmee kostenbesparend zijn. In de afgelopen jaren is in Nederland een sterke stijging te zien van het aantal ziekenhuisopnames vanwege diverticulitis. Kosten voor deze ziekenhuisopnames in Nederland overstijgen reeds de 80 miljoen euro per jaar.[19] Deze toename in ziekenhuisopnames is ook zichtbaar in andere landen. Een Amerikaanse studie liet eveneens een toename in het aantal ziekenhuisopnames zien voor diverticulitis, en dan vooral bij de jongere patiënten.[20] Omdat diverticulitis een recidiefkans van ongeveer 25% kent, en meerdere recidieven bij één en dezelfde patiënt kunnen voorkomen, lopen patiënten met de recidiverende diverticulitis het risico om meerdere CT scans te moeten ondergaan. Dit brengt aanzienlijke kosten met zich mee die zijn geassocieerd met beeldvormende technieken, maar er zijn ook niet onbelangrijke risico's voor de patiënt zoals de blootstelling aan straling en de kans op contrast nefropathie. Verdere validatie van predictie modellen in verschillende subgroepen van patiënten met diverticulitis (i.e., eerste episode, recidief, ongecompliceerd, gecompliceerde diverticulitis, ziekenhuis-populatie, huisartsenpopulatie) is de volgende stap naar het individualiseren van het diagnostische proces van diverticulitis en daarmee de rol van aanvullende beeldvorming inzichtelijker te maken. De toenemende groei van mogelijkheden in "health monitoring", "home biotechnology", en informatietechnologie zullen waarschijnlijk in de nabije toekomst gaan bijdragen aan het zelfmanagement van patiënten met (recidiverende) diverticulitis. Dit zou kunnen leiden tot een reductie van (onnodige) ziekenhuisopnames en de daarmee geassocieerde kosten.[21]

Een van de eerste stappen op dit moment in de reductie van de individuele risico's en het beheersbaar houden van de kosten van patiënten met diverticulitis is het efficiënter gebruiken van de beschikbare diagnostische middelen zoals voorgesteld in de step-up approach, beschreven in dit proefschrift. De step- up approach is een conditionele strategie, waarbij eerst een echografie wordt verricht en een CT scan alleen volgt na een negatieve of niet-conclusieve uitslag van de echografie. De eerste stap in het diagnos-

tische proces is een schatting van de kans op de aanwezigheid van diverticulitis gebaseerd op een klinische evaluatie, en in het ideale geval een schatting van de kans op een gecompliceerde diverticulitis. In het geval van twijfel wordt een echografie verricht. Als de echografie geen duidelijke diagnose geeft of negatief is voor diverticulitis dan wordt een CT scan verricht om de diagnose te stellen. De step-up approach is aantrekkelijk vanuit patiënt- en kostenperspectief, echter geografische verschillen in het gebruik van aanvullende diagnostiek belemmeren algemeen internationaal gebruik hiervan. In een review studie naar het verschil in gebruik van echografie of CT scan voor het diagnosticeren van diverticulitis tussen Britse en Amerikaanse colorectaal chirurgen, kwam een duidelijk verschil naar voren.[22, 23] Minder dan 10% van de Amerikaanse colorectaal chirurgen kozen echografie als de initiële beeldvormende techniek. Dit wordt waarschijnlijk veroorzaakt door de dreiging van medicolegale claims en de hoge prevalentie van obesitas in Amerika. Obese patiënten zijn minder geschikt om echografisch te onderzoeken. In het overgrote deel van Europa wordt echografie verricht door radiologen, maar met de toenemende technologische mogelijkheden van echoapparatuur en de toename van kennis van huisartsen en physician assistants met echografie, kan in de toekomst echografisch onderzoek buiten het ziekenhuis plaatsvinden. Dit kan een verbetering zijn van eerstelijns diagnostiek voor de patiënt, en een mogelijke verlaging van de kosten met zich meebrengen.[24]

De tweede belangrijke vraag is wat de rol is van een chirurgische interventie bij patiënten met meerdere recidieven en chronische pijnklachten. In het verleden werd gedacht dat een chirurgische behandeling van recidief diverticulitis een gecompliceerd recidief en daarmee de kans op een acute operatie kon voorkomen. Tegenwoordig, gebaseerd op meer recentere inzichten, is een chirurgische interventie vooral bedoeld om de klachten die gepaard gaan met recidiverende diverticulitis en chronische pijnklachten tussen de aanvallen door te verminderen.[25-28] Bij sommige patiënten resulteren de chronische pijnklachten tussen de duidelijke aanvallen van diverticulitis door in een soort van chronische ziekte die ook wel symptomatic uncomplicated diverticular disease wordt genoemd (SUDD). SUDD is een subtype van diverticulitis, waarbij er persisterende klachten zijn die worden toegeschreven aan diverticulosis coli zonder dat er een evident macroscopisch beeld van een colitis of diverticulitis is.[29]

Wij concludeerden dat electieve resectie van het colon na twee episodes van diverticulitis niet meer standaard geadviseerd moet worden aan patiënten. Deze conclusie is echter gebaseerd op resultaten van een Markov model, en resultaten van dit model zijn onderhavig aan de validiteit van de data die in het model gebruikt wordt. Met name gegevens uit retrospectieve observationele studies en epidemiologische studies konden worden gebruikt als databron voor het Markov model. Helaas zijn er maar weinig kwalitatief goede studies waar we onze data input op konden baseren. We hebben in de toekomst kwalitatief goede multicentrische gerandomiseerde clinial trials nodig om te beoordelen wat de optimale behandelstrategie is bij patiënten met recidiverende diverti-

culitis of persisterende klachten tussen de aanvallen van diverticulitis door. Met name de rol van electieve chirurgie moet duidelijker worden. Op het moment wordt er een Nederlandse studie uitgevoerd (DIRECT trial), waarbij patiënten met persisterende pijnklachten na een episode van diverticulitis en/of meer dan drie recidieven in twee jaar worden gerandomiseerd tussen chirurgische of conservatieve behandeling. Patiënten die gerandomiseerd worden voor de conservatieve behandeling worden behandeld volgens de nu gangbare protocollen (antibiotica en/of pijnstilling indien noodzakelijk geacht, of afwachtend beleid). Patiënten die gerandomiseerd worden voor een chirurgische behandeling ondergaan een resectie van het aangedane segment van het colon, met health related quality of life (HRQoL) als de primaire uitkomstmaat.[30] Resultaten van deze studie worden in de zomer van 2015 verwacht. Ondanks het feit dat deze trial belangrijke data gaat opleveren over de rol van electieve chirurgie in een goed gedefinieerde studiepopulatie, zal de individuele patiënt waarschijnlijk minder profiteren van de resultaten van deze studie, met name jonge patiënten met een laag operatierisico en oudere patiënten met een hoog operatierisico. Zoals eerder vermeld, zal met name risicoprofilering en het voorspellen van het succes van de behandeling op individueel niveau met behulp van bioinformatietechnologie meer aandacht moeten gaan krijgen, wanneer we verbeteringen in de individuele patiëntenbehandeling willen nastreven. Ondanks dat we naar een meer conservatieve behandeling neigen bij patiënten met recidiverende diverticulitis, laat Hoofdstuk 7 van dit proefschrift zien dat patiënten die een laparoscopische sigmoidresectie hebben ondergaan significante vermindering hebben van gastrointestinale symptomen, vergeleken met de conservatief behandelde patiëntengroep. Met het bewijs van een mogelijk voordeel van een laparoscopische sigmoidresectie, echter wel gebaseerd op een aantal high risk of bias studies, is het belangrijk om de uitkomsten in HRQoL en PROs bij laparoscopische chirurgie voor recidief diverticulitis verder te onderzoeken. Dit soort studies kunnen gedaan worden door grote groepen patiënten te verzamelen (Big Data research). Tegelijk moet dit een stimulans zijn om meer aandacht aan het registeren van patiënten met diverticulitis te besteden, analoog aan de registraties die er zijn voor colorectale maligniteiten gericht op lange termijn resultaten en PROs.

De derde vraag is welke uitkomstmaten belangrijk zijn in het onderzoek naar diverticulitis. Veel gepubliceerde studies focussen op kortetermijnresultaten en uitkomstmaten bepaald door behandelaars en onderzoekers. Gelukkig worden health status en kwaliteit van leven steeds meer erkend als belangrijke uitkomstparameters om het succes van een behandeling voor diverticulitis te bepalen. Veel artikelen gebruiken echter de termen “kwaliteit van leven” (KvL), “health status”, “functionele status”, “health-related quality of life” (HRQoL) en “well-being” (welbevinden) door elkaar.[31] PROs bij patiënten met diverticulitis zijn niet goed gedefinieerd en een belangrijke confounder is dat de patiëntengroep met sympto-matische diverticulosis coli geen homogene groep is, maar een zekere mate van overlap kent met het irritable bowel syndrome (IBS).[29, 32] Begeleiding van de GRADE working group is essentieel voor het gebruik van PROs in systematic reviews. Om de kwaliteit van onderzoek te verbeteren en tot belangrijke conclusies te kunnen komen voor

de individuele patiënt is het essentieel dat we PROs beter definiëren. Het proces van beter definiëren van PROs moet betrekking hebben op patiënten met recidiverende diverticulitis en met persisterende pijnklachten. Patiëntenparticipatie in het ontwikkelen van studie-protocollen heeft recent al geleid tot verrassende (voor behandelaars en onderzoekers) verschuivingen in studiefocus en relevante uitkomstmaten.[33] Om een voorbeeld te geven, vermoeidheid en ongemak van chronisch medicatiegebruik wordt zelden meegenomen in studies, maar kan een cruciale rol spelen in patiënten met recidiverende diverticulitis. De uitkomstmaten die belangrijk zijn voor patiënten kunnen het best ontwikkeld worden door patiëntenfocusgroepen samen te stellen en diepte interviews te verrichten om zo patiënt reported outcome measures (PROMS) en patient reported experience measures (PREMS) te bepalen.[34] PROMS en PREMS zijn niet alleen belangrijk om de kwaliteit van de patiëntenzorg en het evalueren van het effect van bepaalde behandelingen te bepalen, maar spelen ook een belangrijke rol in klinische besluitvorming. Zodra PROMS en PREMS goed gedefinieerd zijn voor patiënten met recidiverende diverticulitis of persisterende klachten, dan kunnen kosten worden bespaard door de gezondheidszorg zo in te richten dat we alleen die behandelingen uitvoeren die de uitkomstmaten van de patiënt daadwerkelijk verbeteren. Dit zal dan uiteindelijk leiden tot een betere waardering van onze gezondheidszorg door patiënten, met een gelijke of mindere kosteninvestering.[34]

De vierde vraag is welke pathofysiologische principes er aan persisterende abdominale pijnklachten en gastrointestinale symptomen na een episode van diverticulitis en na een chirurgische resectie ten grondslag liggen. Als we chronische pijnklachten bij diverticulitis beter gaan begrijpen kunnen we behandelingen daar op afstemmen, en daarmee het aantal chirurgische behandelingen voor diverticulitis verder verminderen. Resultaten van de Markov analyse lieten zien dat bij een vermindering van 73% van de persisterende klachten, 5-ASA en een antibioticum de optimale behandelstrategie in het geval van een recidief diverticulitis werd. Deze reductie in symptomen is beschreven in eerdere studies naar de medicamenteuze behandeling van persisterende klachten en recidief diverticulitis.[13, 14] Ondanks het feit dat persisterende klachten in toenemende mate erkend worden als een belangrijk probleem bij patiënten na een episode van diverticulitis, zijn we nog steeds niet in staat om deze patiëntengroep adequaat te definiëren vanwege een gebrek aan uniformiteit van de definitie van persisterende klachten en een grote verscheidenheid aan gastrointestinale klachten. Persisterende abdominale klachten kunnen ontstaan door viscerale hypersensitiviteit.[35] Abdominale klachten na een sigmoidresectie kunnen ontstaan door bijvoorbeeld een korter segment van de darm (toename van darmperistaltiek), door een relatieve stenose van de anastomose (obstructieve klachten) of door de aanwezigheid van een stoma (lekkage).

De Angelsakische term “diverticular disease” wordt ook wel gedefinieerd als een acute aanval van diverticulitis in een periode van relatieve afwezigheid van de ziekte (diverticulitis), maar dit geldt zeker niet voor iedereen. Sommige patiënten ervaren

chronische pijn, gastrointestinale klachten, of IBS-achtige symptomen die passen bij een chronische darmaandoening.[29] De mogelijkheid dat symptomatische diverticulosis coli beschouwd moet worden als een chronische aandoening is recent in verband gebracht met een verandering in het microbioom van de darm. Een laag-gradige infectie van de mucosa van de darm kan een mogelijke oorzaak zijn voor de klachten die patiënten ervaren bij symptomatische diverticulosis coli en de infectie zelf kan een trigger zijn voor het ontstaan van diverticulitis.[36] Veranderingen in het microbioom van het colon, kan resulteren in pijnklachten, verandering van de motiliteit van de darm of een recidief diverticulitis.[37] Het microbioom in de tractus digestivus van de mens bevat 10^{12} tot 10^{14} genen. De verzameling van deze micro-organismen en hun genetische code wordt het 'microbioom' genoemd.[38] Ondanks het feit dat een verandering in het microbioom bij verschillende aandoeningen is vastgesteld, is het nog niet duidelijk of dit de oorzaak is voor de ziekte of meer een gevolg daarvan.[36] Onderzoek naar de rol van micro-organismen in symptomatische diverticulosis staat in de kinderschoenen.[39] Een recente Nederlandse studie liet zien dat de diagnose diverticulitis met een redelijke goede diagnostische accuratesse kon worden aangetoond op basis van analyse van het microbioom. Het fecale microbioom van patiënten met een eerste episode van diverticulitis verschilde van die van gezonde vrijwilligers. Dit verschil werd vooral veroorzaakt door *Proteobacteria phylum*.[36] Een significant verschil in het voorkomen van *Bifidobacterium longum* en *Bifidobacterium animalis* werd gevonden in een andere serie patiënten met diverticulitis. Helaas was dit een kleine serie van slechts negen patiënten en werden de patiënten in deze studie niet vergeleken met gezonde vrijwilligers.[40] Het vaststellen van een oorzakelijke rol van het microbioom van de darm in symptomatische diverticulosis coli kan belangrijke gevolgen hebben voor de preventie, diagnostiek en behandeling van patiënten met diverticulitis en het meten van het effect van de ingestelde behandeling.[36]

De laatste vraag die beantwoord moet gaan worden is de vraag hoe we richtlijnen aangaande de diagnostiek en behandeling van patiënten met diverticulitis verspreiden, naleven en up-to-date houden. Recente data hebben laten zien dat ondanks de nieuwe inzichten, gepresenteerd in recent gepubliceerde richtlijnen, waarin het advies wordt gegeven niet meer standaard een sigmoidresectie te verrichten na twee episodes van diverticulitis, weinig navolging vindt. Sterker nog, het aantal chirurgische interventies voor patiënten met diverticulitis is fors toegenomen in de laatste twee decennia.[20, 41, 42] Dit kan deels worden verklaard door het gebrek aan consensus tussen richtlijnen onderling en de matige kwaliteit van de data waar de richtlijnen op zijn gebaseerd. Zeer recent is een systematische review verschenen waarin verschillende diverticulitis richtlijnen met elkaar zijn vergeleken.[43] Na het analyseren van alle zes beschikbare richtlijnen (The American Society of Colon and Rectal Surgeons 2006, the Association of Coloproctology of Great Britain and Ireland 2011, de Nederlandse Vereniging voor Heelkunde 2012, the Danish Surgical Society 2011, the European Association for Endoscopic Surgery and the World Society for Emergency Surgery 2013) was er consensus op basis van kwalitatief goede data over:

- De noodzaak van aanvullende beeldvorming in aanvulling op de klinische diagnose
- De overweging om medicamenteus te behandelen alvorens over te gaan op een chirurgische ingreep
- De behandeling van milde diverticulitis in een ambulante setting
- Het gegeven dat electieve chirurgie geen standaard behandeling is
- De voorkeur voor een laparoscopische ingreep in ervaren handen indien er een indicatie is voor een chirurgische behandeling
- Het gegeven dat een laparoscopische peritoneaal lavage tot de behandelmogelijkheden behoort indien conservatieve behandeling van abcesvorming of een Hinchey III diverticulitis faalt

Onderwerpen zonder consensus:

- Optimale classificatie voor de ernst van de diverticulitis
- De eerste keus in diagnostiek voor het diagnosticeren van diverticulitis
- Noodzaak voor coloscopie na een episode van diverticulitis
- Dieetmaatregelen en medicamenteuze therapie
- Antibiotische behandeling
- Chirurgische behandeling voor Hinchey III en IV geperforeerde diverticulitis

Gebaseerd op de systematische review van de verschillende internationale richtlijnen kunnen we concluderen dat over veel onderwerpen binnen diverticulitis nog geen consensus is bereikt of dat er consensus is bereikt maar zonder voldoende wetenschappelijk onderbouwing op basis van kwalitatief goede studies. Dit staat het gebruik van richtlijnen in de weg. Om tot een betere overeenstemming te komen in de diagnostiek en behandeling van diverticulitis is recent een Internationale Diverticulitis Delphi studie voorgesteld door de onderzoeksgroep van Professor Des Winter. Resultaten van deze Delphi studie moeten nog gepubliceerd worden.

Dit proefschrift geeft antwoorden op belangrijke vragen omtrent diagnostiek en behandeling van diverticulitis, maar genereert ook weer nieuwe onderzoeksvragen voor toekomstig onderzoek. Dit toekomstige onderzoek zal zich met name moeten toeleggen op het ontwikkelen van risicoprofielen voor individuele patiënten wat betreft prognose en behandeluitkomsten en uitkomsten die relevant zijn voor patiënten met diverticulitis.

Reference list

1 Rafferty J, Shellito P, Hyman NH, Buie WD, and Standards Committee of American Society of Colon and Rectal Surgeons. Practice parameters for sigmoid diverticulitis. Dis Colon Rectum. 2006, Jul;49(7):939-44.

2 Wexner SD, and Dailey TH. The initial management of left lower quadrant peritonitis. Dis Colon Rectum. 1986, Oct;29(10):635-8.

3 Cho KC, Morehouse HT, Alterman DD, and Thornhill BA. Sigmoid diverticulitis: diagnostic role of CT--comparison with barium enema studies. Radiology. 1990, Jul;176(1):111-5.

4 Farag Soliman M, Wüstner M, Sturm J, Werner A, Diehl SJ, Düber C, and Post S. [Primary diagnostics of acute diverticulitis of the sigmoid]. Ultraschall Med. 2004, Sep;25(5):342-7.

5 Toorenvliet BR, Bakker RF, Breslau PJ, Merkus JW, and Hamming JF. Colonic diverticulitis: a prospective analysis of diagnostic accuracy and clinical decision-making. Colorectal Dis. 2010, Mar;12(3):179-86.

6 Laméris W, van Randen A, van Gulik TM, Busch OR, Winkelhagen J, Bossuyt PM, et al. A clinical decision rule to establish the diagnosis of acute diverticulitis at the emergency department. Dis Colon Rectum. 2010, Jun;53(6):896-904.

7 Laurell H, Hansson LE, and Gunnarsson U. Acute diverticulitis--clinical presentation and differential diagnostics. Colorectal Dis. 2007, Jul;9(6):496-501; discussion 501-2.

8 Miura S, Kodaira S, Shatari T, Nishioka M, Hosoda Y, and Hisa TK. Recent trends in diverticulosis of the right colon in Japan: retrospective review in a regional hospital. Dis Colon Rectum. 2000, Oct;43(10):1383-9.

9 Tursi A, Di Mario F, Brandimarte G, Elisei W, Picchio M, Loperfido S, et al. Intermittent versus every-day mesalazine therapy in preventing complications of diverticular disease: a long-term follow-up study. Eur Rev Med Pharmacol Sci. 2013, Dec;17(23):3244-8.

10 Maconi G, Barbara G, Bosetti C, Cuomo R, and Annibale B. Treatment of Diverticular Disease of the Colon and Prevention of Acute Diverticulitis: A Systematic Review. Dis Colon Rectum. 2011, Oct;54(10):1326-1338.

11 Ünlü C, Daniels L, Vrouenraets BC, and Boermeester MA. A systematic review of high-fibre dietary therapy in diverticular disease. Int J Colorectal Dis. 2012, Apr;27(4):419-27.

12 Raskin JB, Kamm MA, Jamal MM, Márquez J, Melzer E, Schoen RE, et al. Mesalamine did not prevent recurrent diverticulitis in phase 3 controlled trials. Gastroenterology. 2014, Oct;147(4):793-802.

13 Tursi A, Brandimarte G, Giorgetti GM, and Elisei W. Mesalazine and/or Lactobacillus casei in preventing recurrence of symptomatic uncomplicated diverticular disease of the colon: a prospective, randomized, open-label study. J Clin Gastroenterol. 2006, Apr;40(4):312-6.

14 Brandimarte G, and Tursi A. Rifaximin plus mesalazine followed by mesalazine alone is highly effective in obtaining remission of symptomatic uncomplicated diverticular disease. Med Sci Monit. 2004, May;10(5):PI70-3.

15 Richardson WS, and Detsky AS. Users' guides to the medical literature. VII. How to use a clinical decision analysis. A. Are the results of

the study valid? Evidence-Based Medicine Working Group. JAMA. 1995, Apr 26;273(16):1292-5.

16 Basch E. New Frontiers in Patient-Reported Outcomes: Adverse Event Reporting, Comparative Effectiveness, and Quality Assessment. Annu Rev Med. 2013, Nov 20;

17 Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ, and GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008, May 3;336(7651):995-8.

18 Chapman JR, Dozois EJ, Wolff BG, Gullerud RE, and Larson DR. Diverticulitis: a progressive disease? Do multiple recurrences predict less favorable outcomes? Ann Surg. 2006, Jun;243(6):876-830; discussion 880-3.

19 Draaisma WA, van de Wall BJ, Vermeulen J, Unlu C, de Korte N, and Swank HA. [Treatment for diverticulitis not thoroughly researched]. Ned Tijdschr Geneeskd. 2009;153A648.

20 Etzioni DA, Mack TM, Beart RW, and Kaiser AM. Diverticulitis in the United States: 1998-2005: changing patterns of disease and treatment. Ann Surg. 2009, Feb;249(2):210-7.

21 Kohn MS, Sun J, Knoop S, Shabo A, Carmeli B, Sow D, et al. IBM's Health Analytics and Clinical Decision Support. Yearb Med Inform. 2014;9(1):154-62.

22 Schechter S, Mulvey J, and Eisenstat TE. Management of uncomplicated acute diverticulitis: results of a survey. Dis Colon Rectum. 1999, Apr;42(4):470-5; discussion 475-6.

23 Munikrishnan V, Helmy A, Elkhider H, and Omer AA. Management of acute diverticulitis in the East Anglian region: results of a United Kingdom regional survey. Dis Colon Rectum. 2006, Sep;49(9):1332-40.

24 Wong F, Franco Z, Phelan MB, Lam C, and David A. Development of a pilot family medicine hand-carried ultrasound course. WMJ. 2013, Dec;112(6):257-61.

25 Ritz JP, Gröne J, Engelmann S, Lehmann KS, Buhr HJ, and Holmer C. [What is the actual benefit of sigmoid resection for acute diverticulitis? : Functional outcome after surgical and conservative treatment]. Chirurg. 2013, Aug;84(8):673-80.

26 Forgione A, Leroy J, Cahill RA, Bailey C, Simone M, Mutter D, and Marescaux J. Prospective evaluation of functional outcome after laparoscopic sigmoid colectomy. Ann Surg. 2009, Feb;249(2):218-24.

27 Pasternak I, Wiedemann N, Basilicata G, and Melcher GA. Gastrointestinal quality of life after laparoscopic-assisted sigmoidectomy for diverticular disease. Int J Colorectal Dis. 2012, Jun;27(6):781-7.

28 Vermeulen J, Gosselink MP, Busschbach JJ, and Lange JF. Avoiding or reversing Hartmann's procedure provides improved quality of life after perforated diverticulitis. J Gastrointest Surg. 2010, Apr;14(4):651-7.

29 Strate LL, Modi R, Cohen E, and Spiegel BM. Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights. Am J Gastroenterol. 2012, Oct;107(10):1486-93.

30 Van de Wall BJ, Draaisma WA, Consten EC, van der Graaf Y, Otten MH, de Wit GA, et al. DIRECT trial. Diverticulitis recurrences or continuing symptoms: Operative versus conservative treatment. A multicenter randomised clinical trial. BMC Surg. 2010;1025.

31 Johnston BC, Patrick DL, Busse JW, Schünemann HJ, Agarwal A, and Guyatt GH. Patient-reported outcomes in meta-analyses--Part 1: assessing risk of bias and

combining outcomes. Health Qual Life Outcomes. 2013;11(1):109.

32 Cohen E, Fuller G, Bolus R, Modi R, Vu M, Shahedi K, et al. Increased risk for irritable bowel syndrome after acute diverticulitis. Clin Gastroenterol Hepatol. 2013, Dec;11(12):1614-9.

33 Van Bruinessen IR, van Weel-Baumgarten EM, Snippe HW, Gouw H, Zijlstra JM, and van Dulmen S. Active patient participation in the development of an online intervention. JMIR Res Protoc. 2014;3(4):e59.

34 Kaplan RS, and Porter ME. How to solve the cost crisis in health care. Harv Bus Rev. 2011, Sep;89(9):46-52, 54, 56-61 passim.

35 Simpson J, Neal KR, Scholefield JH, and Spiller RC. Patterns of pain in diverticular disease and the influence of acute diverticulitis. Eur J Gastroenterol Hepatol. 2003, Sep;15(9):1005-10.

36 Daniels L, Budding AE, de Korte N, Eck A, Bogaards JA, Stockmann HB, et al. Fecal microbiome analysis as a diagnostic test for diverticulitis. Eur J Clin Microbiol Infect Dis. 2014, Nov;33(11):1927-36.

37 Quigley EM. Gut microbiota, inflammation and symptomatic diverticular disease. New insights into an old and neglected disorder. J Gastrointestin Liver Dis. 2010, Jun;19(2):127-9.

38 Mertz L. My Body, My Microbiome: Microbes outnumber cells, but what are they doing? IEEE Pulse. 2014;5(6):40-5.

39 Hall JF. The microbiome and diverticulitis: a new target for medical therapy? Dis Colon Rectum. 2014, Apr;57(4):544-5.

40 Gueimonde M, Ouwehand A, Huhtinen H, Salminen E, and Salminen S. Qualitative and quantitative analyses of the bifidobacterial microbiota in the colonic mucosa of patients with colorectal cancer, diverticulitis and inflammatory bowel disease. World J Gastroenterol. 2007, Aug 7;13(29):3985-9.

41 Simianu VV, Bastawrous AL, Billingham RP, Farrokhi ET, Fichera A, Herzig DO, et al. Addressing the appropriateness of elective colon resection for diverticulitis: a report from the SCOAP CERTAIN collaborative. Ann Surg. 2014, Sep;260(3):533-8; discussion 538-9.

42 Masoomi H, Buchberg BS, Magno C, Mills SD, and Stamos MJ. Trends in diverticulitis management in the United States from 2002 to 2007. Arch Surg. 2011, Apr;146(4):400-6.

43 Vennix S, Morton DG, Hahnloser D, Lange JF, Bemelman WA, and research committee of the European Society of Coloproctocology. Systematic review of evidence and consensus on diverticulitis: an analysis of national and international guidelines. Colorectal Dis. 2014, Nov;16(11):866-78.

List of publications

List of publications

Recidivering en fistelvorming na incisie en drainage van cryptoglandulaire perianale abcessen.
CS Andeweg, EJ Spillenaar Bilgen, JHG Klinkenbijl.
NTvH 13, nummer 2, april 2004 39-43.

Two patients with retroperitoneal paragangliomas.
JA Wegdam, **CS Andeweg**, QH Leyten, CB Reuvers, EJ Spillenaar Bilgen.
NTvG 2001 okt (20);145:2040-5.

Damage control surgery in polytraumatized patients.
CS Andeweg, N Vingerhoedt, M Haerkens, A van Vugt.
NTvG 2006 jul (8);150:1503-7.

Time to 'rethink the diverticular rules'?
M Cazemier, JA Wegdam, **CS Andeweg**, H van Goor, RP Bleichrodt.
MAGMA jaargang 12, No 1, maart 2006.

Diagnostic Image (318). A man with a non-healing preauricular wound.
CS Andeweg, Th Wobbes.
NTvG 2007 apr (7) ;151:814.

Incidence and risk factors of recurrence after surgery for pathology proven diverticular disease.
CS Andeweg, JH Peters, RP Bleichrodt, H van Goor.
World J Surg. 2008 Jul;32(7):1501-6.

A patient in haemorrhagic shock.
CS Andeweg, AMM Kotsopoulos.
Neth J Crit Care 2009:13(1):41-42.

How to diagnose acute colonic diverticulitis? Proposal for a clinical scoring system.
CS Andeweg, L Knobben, RP Bleichrodt, H van Goor.
Ann Surg. 2011 May;253(5):940-6.

Seroma formation after axillary lymph node dissection in breast cancer surgery: does timing of drain removal matter?
CS Andeweg, MJ Schriek, J Heisterkamp, JA Roukema.
The Breast Journal. 2011 Jul-Aug;17(4):359-64. Epub 2011 Jun 17.

The Transrectus Sheath Preperitoneal Approach (TREPP) for inguinal hernia repair. Rationale and technique.
GG Koning, **CS Andeweg,** MWA van Tilburg, F Keus, CJM van Laarhoven, WL Akkersdijk.
Hernia 2012 Jun;16(3):295-9. Epub 2011 Dec 1.

Guidelines of diagnostics and treatment of acute colonic diverticulitis.
CS Andeweg, IM Mulder, RJF Felt-Bersma, A Verbon, GJ van der Wilt, van Goor H, JF Lange, J Stoker, MA Boermeester, RP Bleichrodt.
Dig Surg. 2013;30(4-6):278-92.

Reply to letter: 'The role of abdominal imaging in cases with a high probability of acute left-sided colonic diverticulitis based on a clinical scoring system'.
CS Andeweg, RP Bleichrodt, H van Goor.
Ann Surg. 2013 Aug;258(2).

Summary of the practice guideline on diverticulitis in the colon: diagnostics and treatment in specialty care.
CS Andeweg, R Felt-Bersma, A Verbon, J Stoker, MA Boermeester, RP Bleichrodt.
NTvG. 2013;157(15):A6124.

External validation of two tools for the clinical diagnosis of acute diverticulitis without imaging.
JS Kiewiet, **CS Andeweg**, H Laurell, L Daniels, W Laméris, JB Reitsma, JCM Hendriks, RP Bleichrodt, H van Goor, MA Boermeester.
Digestive and Liver Disease 2014 Feb;46(2):119-24.

Toward an evidence approach to diagnose acute colonic diverticulitis.
CS Andeweg, JA Wegdam, GJ van der Wilt, J Groenewoud, RP Bleichrodt., H van Goor.
Scandinavian Journal of Gastroenterology 2014 Jul;49(7):775-84.

The disease course of right- and left-sided diverticulitis in a Western population.
JA Wegdam, **CS Andeweg,** TMAJ van Vuuren, TS de Vries Reilingh, HJ van der Zaag-van Loonen, H van Goor.
Submitted

Recurrent colonic diverticulitis: a Markov decision model to guide treatment.
CS Andeweg, J Groenewoud, GJ van der Wilt, RP Bleichrodt, H van Goor
Accepted in Clinical Gastroenterology and Hepatology, March 2015.

Patient reported outcomes in diverticulitis: a systematic review and meta-analysis
CS Andeweg, R Berg, B Staal, RPG van den Broek, H van Goor.
Submitted

Dankwoord

Dankwoord

Als je eenmaal ergens aan begonnen bent dan moet je het ook afmaken, maar in dit geval had ik het van te voren toch niet helemaal overzien. Gelukkig heb ik het niet alleen hoeven doen, en zijn er veel mensen erg behulpzaam en betrokken geweest bij het tot stand komen van dit proefschrift. In een poging recht te doen aan wat een ieders bijdrage aan dit proefschrift is geweest en vooral wat iedereen daarin voor mij betekend heeft, is een dankwoord meer dan op zijn plaats.

Prof. dr. H. van Goor, promotor, Beste Harry, zonder jou was dit proefschrift er niet geweest. Als het tempo weer eens verslofte, wist jij altijd op het juiste moment te motiveren en mij aan te sporen verder te gaan. Ik heb een enorme bewondering voor je als chirurg, opleider en mens. Je bent een echte inspirator, en criticaster, in de goede zin van het woord. Gezegend met een zeer sterk ontwikkeld analytisch vermogen wist je altijd het onderste uit de kan te halen. Soms werd ik er wel eens moedeloos van, alle rode pennenstreken, maar ik heb daarna altijd een goed gevoel gehad als het artikel er weer beter van was geworden. Dit heeft uiteindelijk geresulteerd in dit prachtige proefschrift. Heel veel dank daarvoor.

Prof. dr. R.P. Bleichrodt, promotor en opleider, beste Rob, heel veel dank voor het vertrouwen, toentertijd nog als opleider in het UMC St. Radboud, om mij de fijne kneepjes van de colorectale- en buikwandchirurgie te leren. Tot op de dag van vandaag pluk ik de vruchten van wat u mij hebt geleerd. We zijn samen begonnen aan een eerste artikel over diverticulitis en al snel mondde dit uit in meer ideeën over een beetje het ondergeschoven kindje in de heelkunde. Ik heb met u samen de richtlijn over diverticulitis mogen schrijven, misschien is dat nog wel hetgeen het meest door anderen gelezen wordt, en waar ik het meest trots op ben. Al is het contact veel minder frequent sinds u in het buitenland werkt, ik kan altijd een beroep op u doen. Heel veel dank voor alles.

Geachte leden van de leescommissie, hartelijk dank voor uw tijd en interesse in mijn proefschrift.

Geachte leden van de promotiecommissie, hartelijk dank voor de aandacht en tijd die u aan mijn proefschrift heeft geschonken en voor uw bereidheid te willen opponeren.

Beste Joost,
Eindeloze grappen hebben we kunnen maken over het promoveren, de zin en onzin er van naast de gebruikelijke en vermakelijk anekdotes die we met elkaar delen over het chirurg zijn. Wat hebben we af en toe toch een raar vak, maar geen van ons beiden zou anders willen. Mijn dank is groot voor je onnavolgbare enthousiasme, praktische hulp en onvoorwaardelijke steun als het even tegen zit. Carpe diem, we kunnen nu beiden achterover leunen, ik heb je alleen nog een laatste keer nodig als het om mijn proefschrift gaat.

Lieve Tanja,
Opleidingsvriendinnetje uit Nijmegen, wie had gedacht dat onze levens zo synchroon zouden lopen. Lief en leed hebben we gedeeld in de opleiding en nog steeds. Ik bewonder je enorm voor je duidelijkheid in het maken van keuzes voor je gezin en voor jezelf. Al blijf ik het jammer vinden dat we niet dichter bij elkaar wonen, ik kan me geen lievere en attentere vriendin wensen dan jij. Ik weet dat me niets kan gebeuren als jij bij het verdedigen van mijn proefschrift achter me staat.

Drs. J.A. Groenewoud, beste Hans,
Ons gezamelijke kindje het Markov model heeft me zoveel hoofdbrekens gekost dat ik zowaar grijze haren bij mezelf begon te ontdekken. Of word ik gewoon echt een dagje ouder? Termen als “de toekomst gegeven het heden niet afhangt van het verleden" (zogenaamd makkelijke uitleg van een Markov keten) maakte het er voor mij niet makkelijker op. Terwijl ik er min of meer van overtuigd begon te raken dat ik een gendefect heb voor dit soort statistische tovertrucs, bleef jij volhouden en is het je toch gelukt mij het Markovmodel en aanverwante statistiek op een begrijpelijke manier uit te leggen. Hans, mijn dank is erg groot, dat weet je.

Dr. H.J.M. Oostvogel, beste Henk,
Jij bent voor mij in het tweede deel van mijn opleiding de drijvende kracht geweest achter mijn opleiding tot gastrointestinaal chirurg. Twee keer in de week stonden we gezellig een hele dag samen te opereren, goed op elkaar ingespeeld kon ik altijd met je sparren als het over diverticulitis of wat dan ook ging. “Zie vooral de echt belangrijke dingen in het leven niet over het hoofd” heb je vaak tegen me gezegd. Integer zijn als mens en chirurg met kwaliteit hoog in het vaandel heb ik van je mogen leren. Van jou heb ik de vlakken leren kennen, geleerd nooit de binnenbocht te nemen en een plan B te hebben als het anders loopt dan gepland. Mijn dank is groot.

Opleiders, chirurgen en collega-assistenten uit het UMC St. Radboud in Nijmegen en het St. Elisabeth Ziekenhuis in Tilburg. Dank voor alles wat ik heb mogen leren tijdens mijn opleiding en vooral de gezellige sfeer waarin dit mocht plaatsvinden. Lang leve de gezellige borrels in het St. Anneke, pilsen op de Heuvel in Tilburg en de ongeëvenaarde skitripjes.

Drs. J.A. Wegdam, beste Johannes,
“Er ontbreekt een beetje wegdam-itis,” zeiden ze in Arnhem toen je daar weg was. Need I say more, met jou valt altijd wat te beleven, en jouw bijzondere avonturen werden door menig opleider naverteld. Door jouw enthousiasme en ons eerste gezamenlijke project over neuroendocriene tumoren, waar we allebei volgens mij niet zo veel van begrepen, ben ik verzeild geraakt in de wereld van de chirurgie. Dank daarvoor.

Beste mede auteurs, dank voor de prettige samenwerking bij de totstandkoming van de verschillende artikelen die bijgedragen hebben aan dit proefschrift.

Lieve vrienden en vriendinnen, al hebben jullie inhoudelijk niet bijgedragen aan dit proefschrift, jullie onvoorwaardelijke steun en gezelligheid en luisterend oor waren voor mij super belangrijk. Ik heb wel vaak gehoord “ben je daar nou nog steeds mee bezig”, en ja, dan hoorde ik mezelf weer hetzelfde verhaaltje afsteken, maar dat is nu voorbij. Op naar een nieuw hoofdstuk, en dit keer eentje die niet opgeschreven hoeft te worden.

Maatschap chirurgen Noord-West Veluwe,
Lieve maten, Willem, Rene, Gerrit, Roberto, Marc, Ingjerd, Martin, Annet en Tjeerd. Toen ik in 2010 solliciteerde op een chef plek in jullie maatschap, had ik niet durven dromen zo zacht te landen. Voor toentertijd en nu al helemaal ondenkbaar, nog heel uitzonderlijk dat jullie mij hebben geschoold in de lacunes die ik had in het laparoscopisch opereren en mij in anderhalf jaar tijd tot een volwaardig maatschapslid hebben laten groeien. Ik kan me geen betere maatschap wensen!

Mariska Scheuer, jij verdient een apart plaatsje, formeel geen lid meer van de maatschap en destijds aan mij de eer jou op te volgen. Jij was als een soort moeder voor de maatschap, kwaliteit hoog in het vaandel en koningin van de VIM meldingen. Niet zo gek dat je bij de inspectie bent gaan werken, het ga je goed, maar we houden contact (privé dan hè).

Medewerkers St. Jansdal,
Lieve dames van het secretariaat, OK-assistenten, verpleegkundigen, secretaresses van de afdeling, polimedewerkers, oncologie- en mammacare-verpleegkundigen, en natuurlijk collega-specialisten. Dank voor het altijd maar aanhoren van mijn verhalen over mijn promotie en de morele en soms fysieke ondersteuning die sommigen van jullie hebben geleverd.

Lieve ouders, onvoorwaardelijk is jullie steun. We hadden ons de toekomst wel iets anders voorgesteld, maar desondanks zijn jullie samen een sterk team. Lieve mama, redder in nood, oppas als de vogeltjes nog niet fluiten, rots in de branding en bovenal superlieve oma (superoma) en moeder. Mijn doorzettingsvermogen heb ik van jou gekregen en heeft me gebracht tot waar ik vandaag ben. Lieve papa, ik moet een traantje wegpinken als ik denk aan hoe anders alles had kunnen zijn als het noodlot niet had toegeslagen die ene warme dag in de zomer. Van alle tegenslagen is dit wel de grootste en zijn we die nooit echt helemaal te boven gekomen, vooral jij niet. Dingen niet los kunnen laten, niet accepteren zoals het is zijn misschien de minder mooie eigenschappen die ik van jou heb gekregen, maar trots, eigenheid en vastberadenheid en altijd overal een oplossing voor vinden heb ik in overvloed van je gekregen.

Marike, lief zusje, je bent grappig, slim en vindingrijk. Wie had dat ooit gedacht dat jij als kleine Kiki altijd in de weer met moodboards (voor jou toen nog een plakboek, tijdschrift schaar en wat lijm) zou uitgroeien tot één van Nederlands meest vooraanstaande ontwerpers. Ik ben trots op je! Hoe fijn is het dat onze kinderen zo harmonieus met elkaar opgroeien als nu het geval is. Ik hoop dat we daar nog lang van mogen genieten.

Lieve Chris,
Love you, love you more, love you the most……..

Lieve Emma en Noor en …….
Jullie zijn mijn prachtige oogappeltjes, mijn mooie meisjes. Jullie zijn het mooiste wat me ooit is overkomen.

Caroline

Curriculum vitae

Curriculum vitae

Caroline Suzanne Andeweg was born on the 21st of August 1975 in Ermelo. She grew up in this small town on the Veluwe in the middle part of the Netherlands, with her parents and sister. In 1993, she graduated from the Christelijk College Groevenbeek in Ermelo. Prior to being admitted to medical school, she studied biomedical sciences at the University of Nijmegen (1993-1994). In 1994 she started her medical training at the University of Nijmegen Medical Centre and ended her last in hospital training courses in 2001. During this in hospital training the love for the surgical profession arose. In 2001, after graduating from medical school, she joined the Department of Surgery of the St. Elisabeth Hospital in Tilburg (prof. dr. J.A. Roukema) and later on the Department of Surgery in the Rijnstate Hospital in Arnhem (prof. dr. J.H.G. Klinkenbijl), as a surgical resident. In September 2003, she moved to the Radboud University Medical Centre (prof. dr. R.P. Bleichrodt), where she started her surgical training. At the third year of surgical training she started working on this PhD thesis, which primarily focused on the improvement of the clinical diagnosis and treatment strategies in patients with acute colonic diverticulitis. She is one of the authors of the guideline “Diagnostics and treatment of acute colonic diverticulitis” funded by the Association of Surgeons of the Netherlands in 2012. After completing the first three academic years in surgical training she continued her training in the St. Elisabeth Hospital in Tilburg (prof. dr. C.J.H.M. van Laarhoven and later prof. dr. J.A. Roukema). The last two years of surgical training were focused on gastro-intestinal surgery and surgical oncology. In 2010, after her registration as a surgeon she started working in the St. Jansdal Hospital in Harderwijk, in which she currently holds a staff position as a registered gastrointestinal surgeon and surgical oncologist, with a special interest in minimal invasive colorectal surgery and abdominal wall surgery. She lives in Harderwijk, with Chris Mayland Nielsen and their two daughters Emma en Noor.

Stellingen behorende bij het proefschrift

Changing strategies in diverticulitis

1. “Diverticular disease” is een verwarrende Angelsaksische verzamelterm voor een groot aantal aandoeningen die betrekking hebben op diverticulosis van het colon. Vanwege deze verwarring moet de term worden vermeden in taal en geschrift. (*dit proefschrift*)

2. Aanvullende beeldvorming bij patiënten met een ongecompliceerde diverticulitis leidt zelden tot een verandering in het beleid. (*dit proefschrift*)

3. De combinatie van pijn links onder in de buik, de afwezigheid van braken en een CRP-waarde boven de 50 mg/l heeft een hoge voorspellende waarde voor de aanwezigheid van diverticulitis. (*dit proefschrift*)

4. De “step-up approach”, als eerste een echografie, bij negatieve of niet-conclusieve uitslag gevolgd door een CT scan, is de benadering van keuze voor beeldvorming bij verdenking op een diverticulitis. (*dit proefschrift*)

5. Een electieve sigmoid resectie moet niet meer worden geadviseerd na twee episodes van diverticulitis. (*dit proefschrift*)

6. In het geval van recidiverende diverticulitis moet met de patiënt een individuele afweging worden gemaakt tussen de frequentie en ernst van de klachten en de winst en risico’s van een operatieve behandeling. (*dit proefschrift*)

7. De kwaliteit van leven van patiënten met recidiverende diverticulitis verbetert na een laparoscopische operatie in vergelijking met een conservatieve behandeling. (*dit proefschrift*)

8. Een matig absorbeerbaar antibioticum zoals Ciprofloxacin is een goed alternatief voor chirurgie bij recidiverende klachten na een diverticulitis. (*dit proefschrift*)

9. Jonge leeftijd en persisterende klachten na een chirurgische behandeling voor diverticulitis verhogen de kans op een recidief. (*dit proefschrift*)

10. Artsen zijn nog niet goed in staat om het effect van ziekte en behandeling op kwaliteit van leven te beoordelen. Dit kan leiden tot een “geslaagde” operatie, maar een teleurgestelde patiënt.

11. De kunst is zo te leven dat het je overkomt. (*Martin Bril, 1959-2009*)

12. Nothing is so firmly believed as what we least know. (*Michel de Montaigne, 1533-1592*)

13. Mastering others is strength. Mastering yourself is true power. (*Lao Tzu, 6th century BC*)

Caroline Suzanne Andeweg
30 april 2015